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REGIONAL LYMPH NODE INVOLVEMENT IN SMALL CARCINOMA OF THE CERVIX

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IN THE PAST SEVERAL YEARS, it has become obvious that the prognosis in carcinoma of the cervix depends largely on the extent of the disease at the time of therapy. It has also become clear that within the international classification clinical stage I, in which the carcinoma apparently is confined to the cervix, the best prognosis is seen in those patients with the smallest lesions. Schmitz (6), Corscaden, and Smith have noted that lesions clinically appearing to be 1 centimeter or less in diameter have a more favorable outlook than larger stage I cancers.

Some have speculated that the particularly favorable outlook in these cases is due to the lack of metastases to regional lymph nodes. As long as almost all patients with cervical cancer were being treated with irradiation it was, of course, impossible to confirm or refute this hypothesis. At the present time, with increasing numbers with cervical cancer being treated surgically at various clinics, enough material is at hand to offer at least a preliminary answer.

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MATERIAL AND METHODS

Clinical data were reviewed from all cases of stage I carcinoma of the cervix treated primarily by Wertheim hysterectomy and bilateral pelvic lymphadenectomy from 1939 to 1955 at the Pondville Hospital, the Free Hospital for Women, the Massachusetts General Hospital, the New England Deaconess Hospital, and the Massachusetts Memorial Hospitals. Cases were included in this series if: (1) the lesion was described by the clinician as a carcinoma measuring less than 1 centimeter in diameter, or, (2) the diagnosis of carcinoma was made only after biopsy of a small, suspicious cervical lesion which was not grossly characteristic of cancer.

In the 15 year period covered by this study, there were 193 cases of stage I carcinoma of the cervix primarily treated by Wertheim hysterectomy and bilateral pelvic lymphadenectomy at the hospitals mentioned. Almost half were treated at the Pondville Hospital, and about one-fourth at the Massachusetts General Hospital.

Cases were excluded if the lesion grossly appeared to extend into the endocervical

canal above the external os or if neoplastic epithelium was present in curettings of the endocervix or endometrium. Only those cases were used in which the original examiner believed that all of the lesion had been seen. The decision to include or exclude cases in this series, then, was based solely on the clinical evaluation of the lesion as it was recorded in the hospital chart by the original examiners and not on the pathologic examination of the operative specimen or on the clinical outcome.

After selection of the cases according to these clinical criteria, the pathologic descriptions and, when possible, the microscopic slides of the operative specimens were reviewed. Particular attention was paid to the histologic type of tumor, the number of lymph nodes identified, and the number of nodes containing tumor. From the clinical records, data were also obtained on postoperative complications, recurrence or metastasis of disease, and longevity after therapy.

RESULTS

Forty cases met the criteria for inclusion in this series. The microscopic diagnosis was invasive epidermoid cancer in all of them, although in some cases there were, of course, areas of in situ cancer reported adjacent to the invasive tumor. There were no adenocarcinomas in the group.

From 2 to 36 lymph nodes were identified in each case; the average number was 12. During the 15 years covered, the nodes in these cases were examined and reported in the routine manner of the several pathology laboratories concerned. Additional tissue sections were not prepared in this study.

None of the lymph nodes from these 40 cases contained metastatic carcinoma, and there has been no instance of histologically proved metastasis to distant sites. In 1 case there was a recurrence at the vaginal apex 3 years after the Wertheim hysterectomy and lymph node dissection. This was treated by irradiation and the patient is alive and well 12 years after treatment of the recurrence and 15 years after the initial surgery.

In the group of 153 stage I cancers that were also treated by Wertheim hysterectomy and bilateral pelvic lymphadenectomy during the same period there were lymph node metastases found at operation in 33.

There were 6 deaths in the group of 40 cases. Two patients died within a year after surgery, one from a cerebrovascular accident and one as a suicide. Autopsies were not performed in either case, but clinically there was no evidence of cancer when they were seen at intervals after surgery. One patient died 2 years after a Wertheim hysterectomy with lymph node dissection which revealed a small epidermoid carcinoma of the cervix and 18 negative lymph nodes. Autopsy examination showed a primary, mucin-producing adenocarcinoma of the lung with widespread metastases of this tumor. Neither residual nor metastatic epidermoid carcinoma of the cervix was found. One patient died of adenocarcinoma of the stomach with perforation and peritonitis 3 years after a Wertheim hysterectomy. At autopsy there was no evidence of residual epidermoid carcinoma of the cervix. A fifth patient died 3 years after operation. The cause of death was reported by her physician to be hemothorax. No autopsy was performed and the pathogenesis of the hemothorax was not explained. Six months prior to death she had been examined and no evidence of cancer was found. The sixth patient died 7 years after a Wertheim hysterectomy from carcinoma of the breast, originally diagnosed and treated at the same time as the cervical cancer. Positive axillary lymph nodes were found in the radical mastectomy specimen, and metastatic cancer of the breast, proved by biopsy, was also apparent in other sites before the death of the patient. Although no autopsy was performed, death was attributed by clinicians in charge of the case to metastatic carcinoma of the breast.

All of the remaining 34 patients are alive and well at this time. A local recurrence developed after surgery in only 1 patient, and, as noted before, she was satisfactorily

treated with irradiation. No patient has manifested evidence of metastatic disease. Two have been observed for 4 years, and the remaining 32, for from 5 to 15 years.

Most of the operative and postoperative complications in this series involved the urinary tract, particularly the ureters. Ureterovaginal fistulas occurred in 8 of the 40 cases, and in 11 of the 153 similarly treated cases in which the primary lesion was larger. In 5 cases of the small lesion series, the fistulas healed spontaneously after varying intervals of time, but in 3 others nephrectomies had to be performed. In another case bilateral nephrostomy was performed for ureteral obstruction. Several patients complained of incontinence of varying degree and dysuria for several months after surgery, and long periods of bladder anesthesia and poor function were also commonly seen.

DISCUSSION

For many years clinicians have recognized that with irradiation therapy the prognosis for small carcinomas of the cervix was distinctly better than that for large lesions even though the latter were still confined to the cervix. This fact formed the basis for the Schmitz classification of cervical cancer (6), and for the subdivisions of international stage I advocated by Corscaden.

Finn and Horne have noted on review of all hysterectomies performed at their respective institutions that many microcarcinomas or small invasive carcinomas have been adequately, albeit inadvertently, treated by total hysterectomy alone, without additional surgical or irradiation therapy. In addition, as noted in our patients and those of Schmitz (4, 7), total hysterectomy without node dissection has proved to be adequate therapy for the focally invasive carcinoma that is sometimes found on microscopic examination of uteri which were removed under a diagnosis of carcinoma in situ of the cervix. The longevity of these latter two groups of patients and the lack of development of metastatic cancer strongly suggest that lymph nodes were not involved by tumor at the time of surgery. These findings, plus the relatively good results of irradiation when the cancer is clinically estimated to be less than 1 centimeter in diameter, suggest that this may be the critical size beyond which metastasis to regional lymph nodes and elsewhere in the body is most likely to occur.

The data obtained in the present study support this hypothesis of a 1 centimeter critical size. Metastatic carcinoma was not found in the regional lymph nodes of any of the 40 cases reported here, and in none of these cases has there been clinical evidence of metastatic cervical cancer developing after the Wertheim hysterectomy and bilateral pelvic lymphadenectomy. The critical size, of course, need not be, and in all likelihood would probably not be, exactly the same for all cervical cancers. The same variability would be expected as with any biologic phenomenon.[1] Nevertheless, at least insofar as stage I cervical cancers are concerned, the findings in this study support Wall's contention that the success of treatment depends on the volume of tumor.

[1]After the completion of this study, an exception to the rule was encountered at Roswell Park Memorial Institute in Buffalo. The patient was a 37 year old para 3, gravida 3, white woman first seen on May 19, 1958. She was referred by her private physician after a cervical biopsy specimen was reported to show squamous carcinoma. During the preceding 4 months she had noted occasional intermenstrual vaginal spotting, and some frankly bloody vaginal discharge. She had lost 3 pounds during the same period. Menarche was at age 11 and her menstrual periods had been quite regular prior to the present illness. She was 19 years old when her first child was born and 34 when her third child was born, 3 years before her present illness. Her past history is otherwise noncontributory. Examination of the pelvis showed a smooth cervix with a granulomatous lesion less than 1 centimeter in diameter on the exocervix at 9 o'clock. The lesion was confined to the cervix and the rest of pelvic examination was negative.

Multiple biopsy specimens were taken from the cervix at the 9, 12, 3, 6, and 8 o'clock positions and one from the vagina. Those from the 3 and 8 o'clock positions showed malignant squamous epithelium, but insufficient stroma was present to determine whether there was invasion. The diagnosis on the specimen from the 6 o'clock position was carcinoma in situ with gland involvement. In the specimen from the 9 o'clock site, the tumor was definitely invading the underlying stroma.

On May 29, 1958, a Wertheim hysterectomy with bilateral pelvic lymphadenectomy was performed. During the operation, an enlarged right iliac node 2.5 by 1.5 by 1.0 centimeter containing epidermoid carcinoma was found. No other evidence of metastatic tumor was seen at operation. Gross examination of the cervix showed an area of superficial ulceration measuring approximately 1 centimeter in diameter. Sections through this area revealed well differentiated invasive epidermoid carcinoma, while carcinoma in situ was seen in other areas. Sections from the uterine body did not contain cancer, nor did sections of the ovaries, tubes, 4 additional right iliac and 3 left iliac lymph nodes. The postoperative course was uneventful and the patient was discharged on June 8, 1958.

Of course, other factors than the size of the lesion would also help to determine the presence or absence of metastases. One of these would be the location of the lesion with regard to lymphatic vessels. It has been shown by Stoddard that clusters of invasive cancer cells arising within a field of carcinoma in situ may occasionally penetrate and extend within lymphatics in the cervix. It is therefore to be expected that rarely in cases of microcarcinoma there will be lymphatic extension outside of the cervix with metastases developing in lymph nodes. Indeed, 1 such case has been reported by Decker. The unusual nature of this occurrence, however, is pointed up by the fact that some 3 to 5 per cent of patients with carcinoma in situ may be expected to have microscopic foci of invasive carcinoma (4), yet reports from several clinics do not mention cases with distant metastases occurring years after hysterectomy without node dissection performed for carcinoma in situ.

The recurrence of tumor at the vaginal apex in 1 case 3 years after Wertheim hysterectomy emphasizes the fact that invasive cancer is often found within a field of carcinoma in situ and that occasionally this superficial neoplastic epithelium may extend for some distance over the vaginal wall. In 2 other cases carcinoma in situ extended from the cervix to the line of resection of the vaginal cuff of the hysterectomy specimen. An additional resection of the vaginal wall was done in each case, and in neither case was there a recurrence. The Schiller test, performed at the time of surgery, has been found to be helpful in delineating areas of carcinoma in situ associated with the invasive cancer, and its use should help to avoid leaving behind such areas at operation.

The frequency of urinary tract complications resulting from the surgery is probably a reflection of the radical nature of the hysterectomy itself. The fistulas result from dissection of the ureter and increase with the length of ureter denuded and with the interference with its longitudinal blood supply. The lymph node dissection contributes only indirectly to fistula formation by increasing the dead space and so adding to the inflammatory process generated by the accumulated blood and lymph. The anesthetic, atonic bladders result from interruption of the parasympathetic nerves. The much greater incidence of fistulas, i.e., 20 per cent versus 7 per cent in the very small lesions as compared with larger stage I's, probably is a reflection of the greater ease of dissection in the patients with small lesions. The surgeon tends to perform a dissection that becomes an anatomic exercise.

In this retrospective study, based on available material and records, it has of course not been possible to measure the invasive cancer present in the operative specimens. It is to be hoped that with more frequent detection of cancers while they are still of small size, with increased use of surgery in various centers for the treatment of these lesions, and with more detailed pathologic investigation now being performed on these operative specimens, a study will be forthcoming which will relate the actual size of cervical cancers to the presence of lymph node metastases. Through such a study, confirmation or refutation of this "critical size" concept for regional lymph node metastases will be obtained.

SUMMARY

In a series of 40 surgically treated cases of stage I cancer of the exocervix that clinically appeared to be less than 1 centimeter in diameter, none had regional lymph node metastases. A local recurrence developed in only 1 patient, and this was satisfactorily treated by irradiation. There is no evidence of recurrence in 32 cases 5 to 15 years after surgery, and in 2 cases 4 years after surgery. In the 6 patients who died from 1 to 7 years after surgery, there were no known recurrences, and cancer of the cervix was not the cause of death in any case.

These findings suggest that lymph node metastases are uncommon in cancer of the cervix 1 centimeter or less in diameter. That

such metastases may occur, however, is illustrated by an additional case report in which metastatic cancer was found in an iliac lymph node although the primary lesion did not appear to exceed 1 centimeter in diameter.

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BILATERAL INTERNAL MAMMARY ARTERY LIGATION AND CORONARY ARTERY OCCLUSION

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MOST of the surgical procedures which have been utilized in man in order to increase the effective blood supply to the myocardium have been adopted only after the efficacy of the method has been fairly well established in the experimental animal. For example, abrasion of the epicardium and pericardium, spreading of shredded asbestos over the epicardial surface of the heart, and slowing the venous return by partial occlusion of the coronary sinus or ligation of the great cardiac vein—the essential features of the operation introduced by Beck—have been shown to be of benefit in a number of laboratories by decreasing the mortality rate following ligation of the anterior descending branch of the left coronary artery, decreasing the incidence and size of infarcts, increasing the intercoronary anastomotic circulation as demonstrated by injection studies, and increasing the retrograde coronary flow. In contrast, the small amount of experimental work which has preceded the clinical application of bilateral internal artery ligation has been conflicting in nature and altogether unconvincing.

For this reason, we have undertaken the present study in order to learn whether methods previously shown in this laboratory to have yielded convincing evidence of the efficacy of another procedure would, or would not, demonstrate that the procedure of bilateral mammary artery ligation is of benefit.

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MATERIALS AND METHODS

Healthy mongrel dogs weighing between 5 and 20 kilograms were used. Following induction with thiopental sodium, tracheal intubation was accomplished and an oxygen-ether mixture was administered by a mechanical respirator. Aseptic technique was followed.

In one group of animals, ligation of the internal mammary arteries was performed through a transverse midsternal incision at the level of the second intercostal space. Both arteries were identified and divided between ligatures. Another group of animals was subjected to a similar incision and dissection but no ligation was performed. In both groups of animals, ligation of the anterior descending branch of the left coronary artery was carried out 1 month later. A fourth left intercostal space incision was used, and the anterior descending branch of the left coronary artery was exposed, dissected free, and divided between silk ligatures at its point of origin. In a third group of animals subjected to no previous surgery, the same coronary artery ligation was accomplished.

Careful postmortem study was performed when the dogs died or when they were sacrificed 7 days after coronary division. The left coronary artery was examined carefully, and it was determined whether the septal artery had been occluded by the procedure or whether it had remained patent.

In a few dogs, retrograde coronary flow was measured 24 hours after ligation of the anterior descending branch of the left coronary artery at its origin, both in animals

subjected 1 month previously to bilateral internal mammary artery ligation and in control animals. This procedure was carried out by placing a plastic tube into the distal end of the divided coronary artery and measuring the amount of blood which flowed into a 10 cubic centimeter graduated cylinder during a period of 1 minute.

RESULTS

Ligation and division of the anterior descending branch of the left coronary artery at its origin was performed in 66 dogs (Table I). Group I consisted of 22 dogs which had had no previous surgery. The septal artery was found to have been occluded in 4 of them. Three of these died immediately and the other within 24 hours. Of the remaining 18 dogs, 13 (72 per cent) survived and were sacrificed 7 days after operation. Group II consisted of 27 dogs which were subjected to a similar chest incision and exposure of the internal mammary arteries without ligation 1 month prior to coronary artery division. In 9 of these animals it was found that the septal artery had been occluded. Eight of them died within 24 hours, but 1 survived and was sacrificed 7 days later. Of the remaining 18 dogs, 15 (83 per cent) survived. Group III consisted of 17 dogs which underwent bilateral internal mammary artery ligation a month before coronary artery division. Only 1 septal artery was found to be occluded in this group and this dog died immediately. Nine of the 16 dogs without septal artery occlusion (56 per cent) survived the coronary artery ligation.

Retrograde coronary flow was measured in 7 dogs (Table II). In 3 animals the internal mammary arteries had been ligated a month previously; in 2, a similar chest incision and exposure of the internal mammary arteries without ligation had been performed a month before, and in 2 no prior surgery had been carried out. In each of these three small groups there was considerable variation of flow, but the results in the three groups were altogether similar.

TABLE I.—SURVIVAL STATISTICS IN DOGS SUBJECTED TO LIGATION OF THE ANTERIOR DESCENDING BRANCH OF THE LEFT CORONARY ARTERY

	Group I No surgery	*Group II Chest incision only*	*Group III Bilateral internal mammary artery ligation*
No. of dogs.....	22	27	17
No. with occlusion of septal artery	4	9	1
No. surviving with occlusion of septal artery	0(0%)	1(10%)	0(0%)
No. without occlusion of septal artery...	18	18	16
No. surviving without occlusion of septal artery.....	13(72%)	15(83%)	9(56%)

The average flow in cubic centimeters per minute was approximately 1.7 in the first group, 1.5 in the second, and 2.2 in the third group.

DISCUSSION

The results of these experiments suggest that bilateral ligation of the internal mammary arteries does not provide protection from subsequent ligation and division of the anterior descending branch of the left coronary artery. Indeed, if we consider those animals in which the anterior descending branch of the left coronary artery was divided and ligated without occlusion of the septal artery, we find that only 56 per cent of the group subjected a month beforehand to internal mammary artery ligation survived, as compared with 72 per cent in the untreated controls, and 83 per cent in those subjected a month previously to a sham operation. Practically all of the animals in which the septal artery had been occluded died following coronary artery ligation. Glover and his associates reported that 58 per cent of the dogs with prior bilateral internal mammary artery ligation survived coronary artery ligation, and only 1 of 14 control dogs. They thus considered their experiments indicative of protection afforded by this procedure. Lord and his

colleagues (8), measuring coronary blood flow during extracorporeal circulation, reported that an increase in coronary flow was apparently demonstrated in half of 8 dogs subjected to bilateral internal mammary artery ligation. Later and more extensive studies utilizing the same technique, however, have convinced these investigators that no real increase in coronary flow is demonstrable following bilateral internal mammary artery ligation (7). Blair, Roth, and Zintel, in attempting to measure coronary flow with extracorporeal circulation, reached the conclusion that acutely clamping the internal mammary arteries effected no change, but that in 5 dogs subjected to bilateral internal mammary artery ligation 6 months previously, an increase in coronary flow was apparent. Griffin, Hardy, and Turner were able by dye injection studies to show some vascular connections between the internal mammary artery and the pericardium, as Battezzati and his associates had earlier (1, 3). However, they demonstrated little, if any, evidence of significant flow from the ligated internal mammary arteries into the coronary circulation. It was found that 0.25 cubic centimeter of a saturated solution of potassium chloride injected into the left ventricle with momentary clamping of the ascending aorta produced cardiac arrest in all normal dogs, and that 0.1 cubic centimeter of the same solution produced arrest in 75 per cent of normal dogs. In contrast, the injection of a far larger quantity of saturated potassium chloride into the internal mammary artery failed to produce cardiac arrest in 6 dogs previously subjected to right internal mammary artery ligation and in only half of 8 dogs in which the left internal mammary artery had been previously ligated. Taber and Marchioro have recently reported that they noted a rise in subclavian arterial pressure when the internal mammary arteries were occluded. This is a most peculiar observation and one difficult to assume significant, as pointed out in the discussion of this paper by Swan. Swan remarked that, in a similar experiment utilizing much larger arteries where any effect of this sort would apparently be more manifest, he had been unable to observe any rise in pressure. With strain gauge manometer recordings of aortic pressure, no such rise had been observed when any major branch of the aorta was ligated, including the femoral and subclavian arteries. It would seem most doubtful that the observations of Taber and Marchioro could be utilized to support the hypothesis that internal mammary artery ligation actually could be expected to increase coronary flow. In a recent excellent study, Sabiston and Blalock measured internal mammary artery flow immediately after ligation and at intervals of weeks after ligation. The volume flow was found to be very small, with low values for back pressure and back flow. They found that blood flow in the internal mammary artery was increased significantly when concomitant ligation of the remaining branches of the subclavian artery was performed, but, in spite of the increase in flow, back pressure, and back flow observed, no protection seemed to be afforded the heart when the anterior descending coronary artery was ligated. The mortality in their hands ranged from 78 to 93 per cent following ligation of the anterior descending coronary artery in the three groups studied, those with acute ligation of the internal mammary artery, those with chronic bilateral ligation of the internal mammary arteries, and those in which the internal mammary arteries and the other branches of the subclavian artery had been ligated some time prior to the test procedure.

One feature of our current study is puzzling and in a sense distressing. In 3 previous studies in which ligation of the anterior descending branch of the left coronary artery was performed, the results were quite consistent with regard to the mortality observed in untreated and presumably normal mongrel dogs. The overall mortality observed in the control animals in these 3 experiments was 66 per cent, and the mortality in those in which the septal

artery remained patent was 57.5 per cent. The over-all mortality in the untreated control group in the present study was only 40 per cent, and that in the group in which the septal artery remained patent only 28 per cent. Why in this particular study the control mortality should have been so much less than in our previous studies, we do not understand. All the experiments were performed in the same laboratory. The method of intubation, the anesthesia, and the operative technique were unchanged. To be sure, the operations performed in the present study were carried out by individuals other than those who did the operations in the earlier studies. Since, however, the operative technique was just the same, and since careful postmortem studies in all the experiments revealed that the anterior descending branch had indeed been divided between ligatures at the point of origin, it is difficult to understand why this should have made any difference whatsoever. The only factor which may have pertinence relates to the fact that most of the animals in the earlier studies were kept in cages, whereas during the present study they were kept in large pens. In spite of the fact that there is no clear-cut explanation of why in several earlier experiments the mortality was higher than it was in this one, we do not believe that the meaningfulness of the current study is vitiated. Rather, these results emphasize again the necessity for carrying out control observations concurrently during any study designed to test the value of any given procedure in providing the myocardium with more effective circulation.

From our own experiences, and those reported by others, it seems evident that there is no real experimental basis for assuming that bilateral internal mammary artery ligation can be expected to bring about improved myocardial circulation. It would therefore seem unwise to utilize this procedure in the treatment of patients, particularly since other methods have both a good experimental and clinical basis to support their use.

TABLE II.—RESULTS OF MEASUREMENT OF RETROGRADE CORONARY FLOW 24 HOURS AFTER LIGATION OF ANTERIOR DESCENDING BRANCH OF LEFT CORONARY ARTERY

"Protective" procedure	*Dog No.*	*Weight in kgm.*	*B.P. in mm. Hg*	*Flow in c.c./min.*
None	1	12	100	3.8
			100	3.0
	2	12	100	0.9
			100	1.0
Average				2.2
Sham operation 1 month previously	3	11	75	0.9
			75	0.8
	4	12	80	2.0
			80	2.2
Average				1.5
Ligation internal mammary arteries 1 month previously	5	10.5	90	1.0
			90	0.9
	6	13.2	115	3.6
			120	3.6
	7	7	75	0.4
			75	0.6
Average				1.7

SUMMARY

Animal experiments failed to demonstrate that bilateral ligation of the internal mammary arteries performed 1 month previously provided any protection against division of the anterior descending branch of the left coronary artery. The survival rate was quite as good in untreated controls and in animals previously subjected to a sham operation. No increase in retrograde coronary flow was demonstrated in animals a month after bilateral internal mammary ligation as compared with animals in the other two groups.

Our experiments and a survey of those reported in the literature yield no convincing experimental basis for applying the procedure of internal mammary artery ligation to man.

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FUNCTIONAL STUDIES ON TRANSPLANTED INTESTINAL SMOOTH MUSCLE GRAFTS USED TO RECONSTRUCT THE DENERVATED CANINE BLADDER

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SMOOTH MUSCLE is a rather primitive muscular tissue whose principal function is to provide motion for hollow viscera and vasculature. Studies on the function of this tissue have given us much useful information. Many of these investigations, however, are concerned with the microscopic or biochemical study of the dead tissue or the pharmacologic evaluation of the response of the isolated muscle cell in vitro. Methods or preparations for the study of smooth muscle function in vivo have not been extensively investigated; furthermore, the functional adaptations of transplanted smooth muscle have been largely ignored.

Our present efforts have been directed toward a study of the adaptations of intestinal smooth muscle transplanted into the bladder. Thus, it is hoped that the altered physiologic environment and increased functional demands may further elucidate biologic capabilities of this important tissue. The preparation studied involved the denervated canine bladder reconstructed with intestinal smooth muscles in the form of a reversed seromuscular graft; this graft, previously described in detail (4), consists of an intestinal segment, with its intact neural and vascular connections carefully preserved in the mesenteric pedicle, but stripped of its mucous membrane, and reversed so that the serosal surface faces inward toward the lumen of the reconstructed organ. Within 2 or 3 weeks the graft becomes lined with stratified transitional cell epithelium. The two-layered muscular architecture of the intestine breaks up into smaller muscular bundles which, gradually over a period of 3 to 6 months, become interlaced in a plexiform network morphologically indistinguishable from normal detrusor muscle. Normal function of the reconstructed bladder was demonstrated by standard urologic functional tests. Instillation of radioactive sodium, iodide, and phosphate into this type of reconstructed bladder demonstrated ion transport patterns comparable to normal. The innervation of the reconstructed bladder has been demonstrated to be derived from the vagus nerve (3). In a preliminary study (5) the bladders of a series of dogs were denervated by pelvic neurectomy and dorsal rhizotomy and then reconstructed. In the present study, observations, functional tests, and cystometrograms are compared in the following groups: (1) the normal intact dog; (2) the normal dog whose bladder has been reconstructed with a reversed seromuscular ileal graft; (3) dogs whose bladders were denervated by pelvic neurectomy, dorsal rhizotomy, cauda equina section, and spinal cord transection; (4) dogs with bladders so denervated and then reconstructed.

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MICTURITION PATTERNS, FUNCTIONAL TESTS, AND CYSTOMETRY IN NORMAL AND RECONSTRUCTED BLADDERS

Observations were carried out on 8 normal dogs and on 14 dogs whose bladders

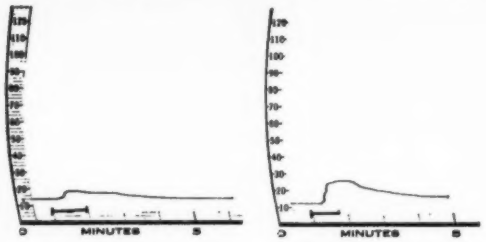

FIG. 1. Intravesical pressure in millimeters of mercury in dog 12, 4 months after bladder reconstruction. a, left, The short line represents the period of stimulation with 20 volts to the right vagus nerve. b, right, The short line represents 50 volt stimulation to the left vagus nerve.

were reconstructed with reversed seromuscular grafts from the ileum and colon. In the latter group, the animals were studied from 2 months to 2 years after operation. During this time careful observations of their voiding habits revealed no instance of incontinence or departure from normal voiding behavior. The leg raising reflex of the 6 male dogs persisted. Catheterizations were performed immediately after voiding in each of the animals of both groups. In no instances were significant amounts of residual urine found. Excretory urograms and cystograms demonstrated good structure and function. Essentially normal cystometrograms were found in the normal animals as well as in the animals with reconstructed bladders when tested without anesthesia or under very light pentothal sodium administered intravenously.

STUDIES ON THE INNERVATION OF THE RECONSTRUCTED BLADDER

Methods. Studies were made on a series of 9 normal intact dogs, 14 dogs whose bladders were reconstructed with reversed seromuscular grafts from the ileum and colon, and 3 dogs whose bladders were reconstructed with the classical nonreversed ileal segments. Contraction of the detrusor muscle as evidenced by increased intravesical pressure was measured with a water manometer and a Lewis recording cystometer before and after stimulation of the vagus and pelvic nerves. In order to obviate changes in the intravesical pressure due to respiration or contraction of the abdominal musculature, the abdomen was opened in the midline under very light pentothal sodium anesthesia, and a large self-retaining retractor was used to separate the recti. In a few instances, the rectus tendon and fascia were severed from the pubic arch.

The nervi erigentes were exposed at the point of entry into the pelvic cavity and the vagi, through a midline cervical incision. These nerves were stimulated with shield electrodes and an electrodyne stimulator using voltages ranging from 2 to 100 volts and a frequency of 100 stimuli per second.

Results. Following vagal stimulation in the normal dog, there was no change in the intravesical pressure and no observable activity of the detrusor muscle. Stimulation of the pelvic nerves in these dogs elicited an immediate increase in intravesical pressure.

After both right and left vagal stimulation in the dogs with reversed ileal grafts, there was a latent period varying from 20 to 90 seconds depending on the voltage and the interval between stimulations. Following this latent period there was a definite rise in intravesical pressure to as high as 16 millimeters of mercury and prominent muscular activity was visible throughout the graft (Fig. 1). Stimulation of the pelvic nerves produced no significant pressure change or visible muscular activity.

To rule out the remote possibility that the electrical impulse may have traveled in routes other than the vagus nerve, the sternohyoid and rectus muscles were stimulated; there was no response. The mesenteric pedicle of the graft with its neurovascular connections to the reconstructed bladder was then severed and the series of vagal stimulations repeated. Again, there was no visible muscular activity and no increase in intravesical pressure. Stimulation of the mesenteric pedicle before it was severed and stimulation of the grafted muscle itself produced an immediate contraction.

In dogs whose bladders were reconstructed with segments of colon, there were no

significant pressure elevations after vagal stimulation. Stimulation of the pelvic nerves after a short latent period elicited a pronounced increase in intravesical pressure.

In animals whose bladders were reconstructed with a nonreversed intestinal segment, vagal stimulation produced the expected rise in intravesical pressure. The muscular activity of the graft was observed as peristaltic waves which arose on one side of the graft and spread to the remaining portions. Coincident with this visible peristaltic contraction was a slow and sometimes irregular increase in intravesical pressure. By contrast vagal stimulation of those animals with reversed ileal bladder grafts produced a concerted or uniform muscular contraction and a corresponding increase in intravesical pressure, but with no evidence of peristaltic waves. The previously described morphologic changes occurring in the reversed seromuscular bladder graft may explain this difference: the two smooth muscle layers of the intestinal wall break up into small fasicles which later become interlaced in a plexiform network. Contraction at the fibers of such a network produces an integrated contraction of the whole organ, as occurs in the normal bladder.

Evidence from these electrical stimulation experiments indicates that the efferent nerve supply to the bladder reconstructed with reversed ileal grafts occurs through the vagus nerve. Presumably vagal impulses modify, integrate, and modulate the smooth muscle activity which formerly gave rise to peristaltic motion and now results in micturition.

DENERVATION OF THE BLADDER: CHANGES FOLLOWING PELVIC NEURECTOMY, DORSAL RHIZOTOMY, SECTION OF THE CAUDA EQUINA, AND SPINAL CORD TRANSECTION

Method. Four types of neurologic lesions were produced in 20 dogs.

1. In 9 animals the nervi erigentes were exposed opposite the base of the bladder and traced back to their entrance to the pelvic cavity at or near their origin from the spinal nerves. They were sectioned close to their origins and the proximal end turned back and tied onto itself so as to impede regeneration. The nerves were stimulated before and after sectioning.

2. In 3 dogs extradural section of the posterior roots from the first to the fourth sacral nerves inclusive was performed after a routine laminectomy.

3. In 1 dog, section of the cauda equina was performed.

4. In 7 dogs the spinal cord was transected: 3 at the level of the first lumbar nerve, 2 at the level of the third lumbar nerve, 1 at the level of the fifth lumbar nerve, and 1 at the level of the sixth lumbar nerve.

Results. Observations following these procedures revealed the abnormal patterns of micturition such as have been reported previously. Incontinence, periodic micturition, and retention of urine developed within a few days. Cystitis was a prominent complication; stasis with macroscopic precipitation of crystals was commonly observed. In all animals, there was evidence of marked vesical dysfunction with either constant dribbling or frequent periodic micturition (every 5 to 10 minutes) of small amounts of urine. The animals exhibited lethargy, fever, poor appetite, and lack of interest in their surroundings. During the period of observation prior to reconstruction, 5 animals died; at postmortem examination evidence of ascending pyelonephritis was present. This observation is consistent with the findings of Dees and Langworthy who reported 52 per cent mortality within 14 days in cats subjected to dorsal rhizotomy.

Following pelvic neurectomy the usual pattern was that of a spastic or hypertonic bladder with small capacity and residual urine. At operation or autopsy the vesical wall was markedly hypertrophied in all instances. On histologic study there was a profuse infiltration of the epithelial and subepithelial layers with inflammatory cells, and the muscular elements appeared to be

TABLE I.—SUMMARY OF DATA

	BEFORE DENERVATION		AFTER DENERVATION									AFTER RECONSTRUCTION						
No.	*Micturition pattern*	*Capacity, c.c.*	*Denervation procedure*	*Date, 1956*	*Capacity, c.c.*	*Residual, c.c.*	*Infection*	*Continence*	*Cystometric pattern*	*Period of observation, days*	*Remarks*	*Date*	*Capacity, c.c.*	*Residual, c.c.*	*Infection*	*Continence*	*Period of observation*	*Remarks*
48	Normal	90	Pelvic neurectomy	11–25	250*→225		Slight	2–10c.c. q. 5 min.	Atonic	18		12–23	45→ 70	2→12	Some clearing with Rx.	Continent	5 months	Satisfactory result
1203	Normal	120	Pelvic neurectomy	11–25	45→ 50	40	Slight	Dribbling	Hypertonic	32		12–28	100	0	Slight	Continent	1 month	Satisfactory result
2	Normal	85	Pelvic neurectomy	11–26	Reconstructed immediately after denervation							11–26	60	0	Trichomonas	Continent	6 months	Persistent infection
1214	Normal	120	Pelvic neurectomy	11–27	125→100		Present	Incontinent		19	Died before reconstruction							
1095	Normal	115	Pelvic neurectomy	12–4	285→ 85		Present	Incontinent	Atonic, then hypertonic	36		1–9	80→135	2→ 5	Slightly cloudy urine	Continent	5 months	Satisfactory result
1264	Normal	125	Pelvic neurectomy	12–24	125		Present			5	Died before reconstruction							
20	Normal	225	Pelvic neurectomy	12–29	175→ 60		Present	Dribbling	Hypertonic	15		1–13	150→200	10	Some	Continent	4 months	Satisfactory result
12	Normal	75	Pelvic neurectomy	12–29	60→ 37		None	Dribbling	Hypertonic	12		1–10	65→ 75	2–4	Some	Continent	4 months	Satisfactory result
44	Normal	250	Pelvic neurectomy	1–31			Present	Dribbling		3	Died before reconstruction							
1208	Normal	100	Dorsal rhizotomy	12–16	50→120	10→50		Dribbling	Hypertonic	11		12–27	85→110	0–3	Slight	Continent	5 months	Satisfactory result

*→Indicates a progressive change over the period of observation, in this instance from 250 to 225 c.c.

TABLE I.—SUMMARY OF DATA—Continued

*→Indicates a progressive change over the period of observation, in this instance from 250 to 225 c.c.

TABLE I.—SUMMARY OF DATA—Continued

	BEFORE DENERVATION		AFTER DENERVATION								AFTER RECONSTRUCTION						
No.	*Micturition pattern*	*Capacity, c.c.*	*Denervation procedure*	*Date, 1956*	*Capacity, c.c.*	*Residual, c.c.*	*Infection*	*Continence*	*Cystometric pattern*	*Period of observation, days*	*Remarks*	*Date*	*Capacity, c.c.*	*Residual, c.c.*	*Infection*	*Continence*	*Period of observation*	*Remarks*
42	Normal	150	Dorsal rhizotomy	1–4	250*→210	10	Minimal	Dribbling	Atonic	32		2–6	125	0–6	Moderate	Continent	4 months	Some persistent infection
4	Normal	75	Dorsal rhizotomy	1–7	112→265	20		Dribbling	Atonic	21		1–25	45→ 30	4–12	Marked	Incontinent	4 months	Technical error
46	Normal	230	Cauda equina section	12–31	475→575	120	Slight	Dribbling	Atonic	13		1–13	175→150	2	None	Continent	18 months	Satisfactory result
1226	Normal	125	Cord section L3	12–20	600	470		Dribbling	Atonic	7	Died before reconstruction							
16	Normal	75	L5	2–7	250→ 50	35→ 5	Slight	Dribbling	Atonic, then, hypertonic	21		2–28	60→ 50	5	Present	Continent	3 months	Persistent infection with some lack of development of capacity
32	Normal	105	L1	4–14	150	50		Dribbling	Atonic	5	Died before reconstruction							
25	Normal	105	L1	4–28	Reconstructed 4 months prior to denervation							1–7	100	0	Slight	Continent	10 days	
9	Normal	100	L1	5–10	Reconstructed 3 months prior to denervation							1–28	100	0	Slight	Continent	2 weeks	
13	Normal	140	L3	11–27	475	430	Marked	Dribbling	Atonic	8		12–4	40		Moderate	?	6 weeks	Extensive ulceration of hind legs; exp. terminated
449	Normal	165	L6	12–3	80	19	Marked	Dribbling	Hypertonic	10		12–13	50	10	Present	?	14 months	Persistent infection with failure to develop bladder capacity

*→Indicates a progressive change over the period of observation, in this instance from 250 to 210 c.c.

excessively hypertrophied. Cystometric observations were not consistent. A spastic type cystometrogram was found in 4 or possibly 5 dogs. One of these (dog No. 1095) exhibited a hypotonic pattern for 30 days. Within 24 hours after the cystometrogram was performed on the thirtieth postoperative day, the urine, which had been clear, turned frankly purulent, and shortly thereafter a hypertonic pattern was found by cystometry. This is interpreted as a demonstration of the effect of local factors, such as infection, upon the tone of the bladder. In 2 dogs the cystometric pattern was that of a hypotonic bladder with capacities of 285 and 250 cubic centimeters with residual urines of over 50 cubic centimeters.

Two of the 3 animals subjected to dorsal rhizotomy exhibited an atonic cystometric pattern, while 1 showed a hypertonic bladder. In the animal with the cauda equina lesion an atonic cystometric pattern developed. In most, but not all, of the animals with cord transections an immediate dilatation developed postoperatively (the so-called stage of spinal shock), but later the bladder reverted to the hypertonic spastic type seen after complete cord lesions. Table I summarizes the data observed before and after the various types of denervation.

RECONSTRUCTION OF DENERVATED BLADDER

Method. Following denervation of the bladder by the methods outlined, the animals were observed for 1 to 4 weeks in order to demonstrate the functional impairment. No antibiotics or preoperative preparation was given, and no attempt was made to sterilize the urinary tract even in the animals which appeared septic. Subtotal resection of the denervated bladder and reconstruction with reversed seromuscular ileal grafts were performed on the 15 dogs surviving the denervations and the observation period, and the animals were followed for from 10 days to 18 months.

Results. The results are summarized in Table I. There was no mortality. Frequently animals that were febrile and appeared sick after their denervation procedure improved clinically after reconstruction of their bladder. Dribbling of urine occurred for several weeks after removal of urethral and suprapubic tubes. However, after the passage of a variable period of time continence developed. Two dogs whose bladders were reconstructed after pelvic neurectomy appeared to be continent as soon as 2 weeks after reconstruction. They voided 80 to 100 cubic centimeters at a time, with no intermittent dribbling between times. In most animals, however, 1 to 3 months were required for continence and satisfactory capacity to develop. The period depended largely upon the amount and severity of the infection which was present when reconstruction was undertaken or developed during the postoperative period. Catheterization after voiding revealed no significant residual urine. Figures 4, 5, and 6 illustrate cystometrograms from representative animals whose bladders were reconstructed following denervation by pelvic neurectomy, dorsal rhizotomy, and cauda equina section.

Of the 7 dogs subjected to cord transection 2 animals died before reconstruction could be accomplished, 1 at 5 days and 1 at 7 days. Two animals were grafted prior to cord transection (at the level of the first lumbar) and followed for 10 days and 2 weeks postoperatively. This variation was found necessary in the higher lesions because of the difficulty in keeping the paraplegic animals alive and in a reasonable state of health under the existing laboratory conditions. Both of these animals showed little change of cystometric pattern (Fig. 7). In 3 animals the cord lesions were created first (1 at the third, 1 at the fifth, and 1 at the sixth lumbar level) and after the development of the neurogenic bladder reconstruction was undertaken. The dog with the lesion at the third lumbar level did well postoperatively, the constant dribbling of urine was coming under good control, and the perineum was no longer constantly wet; however, when both hind legs became involved in extensive ulcerations, the experi-

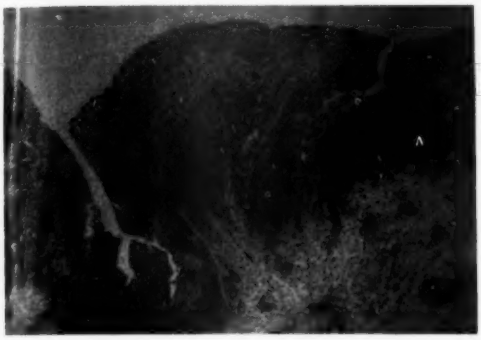

FIG. 2. Section of neurogenic bladder 20 days after pelvic neurectomy showing marked inflammatory reaction with cellular infiltration of the subepithelial layer. Medium power, hematoxylin and eosin.

FIG. 3. Photomicrograph of the epithelial layer of reconstructed bladder showing transitional cell epithelium 3 weeks following operation. High power, hematoxylin and eosin.

ment was terminated and the dog sacrificed. The 2 remaining dogs with cord lesions have done well, are continent, and do not lose urine on standing on all four legs or when held in an upright posture. Both, however, have somewhat limited capacity (50 to 60 c.c.) incident to a persistent urinary tract infection.

In 1 of the dogs whose bladder was reconstructed, the mesenteric pedicle to the bladder graft was severed after the dog was found to have a normal voiding pattern. Neurogenic dysfunction of the bladder promptly developed with a capacity of 35 cubic centimeters, residual urine, incontinence, and a hypertonic cystogram. The graft was excised and the bladder was reconstructed a second time. The dog now has good control with no dribbling and satisfactory capacity (Fig. 8).

DISCUSSION

Smooth muscle is a plastic tissue which adapts itself so specifically to the various functions of the organs in which it appears that many of its characteristics are best observed by a study of the functions of the organs themselves. The study of isolated tissue, though serving a measure of usefulness, is limited, and interpretation of the information derived is difficult. The separation of the muscle from its neural component, while appealing to the anatomic eye, may, nevertheless, be regarded as an arbitrary and nonphysiologic dissection. The functional unit is quite clearly the smooth muscle cell together with its primary reflex arc; it is impossible with our present understanding to separate the purely neural from the purely muscular. Thus, consideration of a concept of the neuromuscular unit as the functional instrument is in order.

Unsuspected physiologic capacities of smooth muscle tissue may be elicited by transplanting this tissue and its intact neural communications. Under the circumstances of this type of transplantation, the altered environment of the new site or organ into which the smooth muscle graft is transplanted produces increased physiologic demands and evokes alteration of smooth muscle responses.

In many respects the bladder is an ideal organ to study. It is almost a surface organ; it can easily be looked into, biopsied, catheterized, or its pressure can be measured. A large body of information on functional tests and measurements has been accumulated over the past half century or more in both animals and man. The effects of various types of denervation have been studied experimentally and clinically. Normality is found throughout a very narrow range of functional activity; with relatively

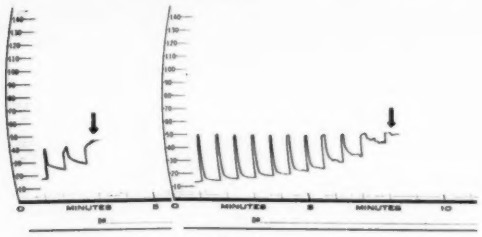

FIG. 4.

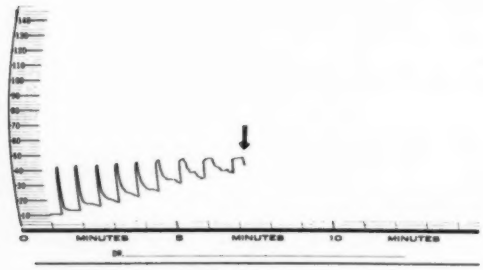

FIG. 5.

FIG. 4. Cystometrograms of dog 1095. a, left, Thirty-two days after pelvic neurectomy; capacity 35 cubic centimeters; incontinent. b, right, Three months after reconstruction; capacity 130 cubic centimeters; continent. Increments of filling 12.5 cubic centimeters. Arrows indicate voiding around catheter.

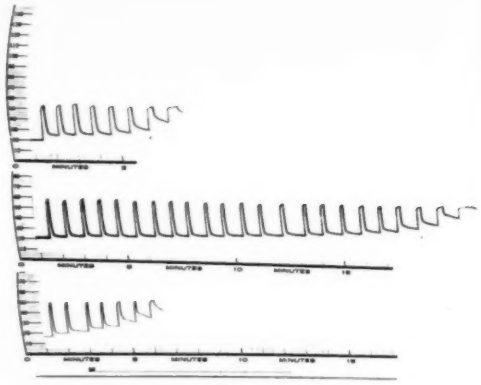

FIG. 6.

FIG. 5. Cystometrogram of dog 1208, 3 months postreconstruction and 3½ months following dorsal rhizotomy. Initial capacity 150 cubic centimeters, after dorsal rhizotomy 250 cubic centimeters, and after reconstruction 125 cubic centimeters. Filling increments 12.5 cubic centimeters. Arrow indicates voiding around catheter.

FIG. 6. Cystometrograms of dog 46. Upper tracing, initial cystometrogram on intact animal; capacity 175 cubic centimeters. Middle tracing, 13 days after cauda equina section; 575 cubic centimeter capacity with 120 cubic centimeter residual urine; incontinent. Lower tracing, 3 months after reconstruction; capacity 150 cubic centimeters; 25 cubic centimeter filling increments in all three tracings.

minor derangements marked functional changes are apparent.

Taken as a whole the findings of these studies may appear difficult to interpret; individually, however, the results are readily explicable. Growth of epithelium over the surface of the graft may be considered an expected finding; epithelization of a plastic or a nonviable tissue, such as free fascial grafts, implanted into the bladder has been reported by De Muth and associates (1). Epithelial growth proceeds more rapidly, however, upon viable tissue. If serosal surface is presented to the inner surface of the bladder, the natural resistance to infection afforded by this peritoneal structure further encourages epithelial overgrowth. Changes in the architecture of the two layered intestinal smooth muscle to a plexiform network have been followed serially in the aging graft. Rearrangement or realignment of these muscle fascicles is probably accountable as a physiologic adaptation induced purely by mechanical factors. These structural changes do not take place when the intestinal mucous membrane and tough submucosal layer are allowed to remain as the inner lining of the newly fashioned bladder.

The character of the response to electrical stimulation of the nerve supply is such as to suggest that the myotatic and myotonic reflexes, which in the native intestine were operative to produce the several types of peristaltic activity, have been modified to give rise to an integrated muscular activity simulating the normal vesical contraction. This fact may be partly explained by the alteration in the architecture of the smooth muscle, though it must also represent, in some measure, other physiologic adaptations. The reflexes governing micturition in the bladder reconstructed with the reversed seromuscular intestinal graft are mediated

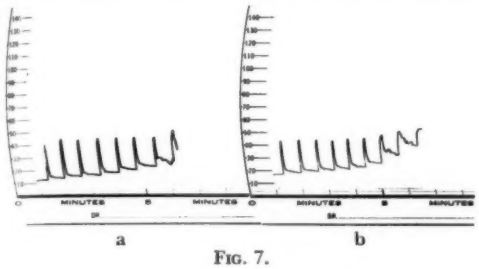

FIG. 7.

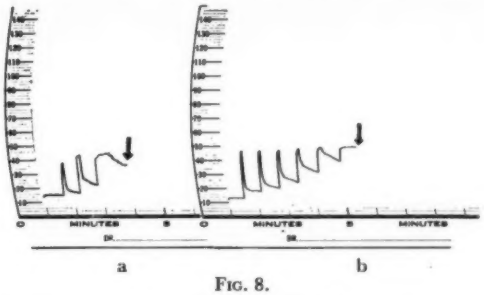

FIG. 8.

FIG. 7. Cystometrograms of dog 32, 3 months after reconstruction. a, Before cord section; b, 10 days after cord section at first lumbar; 12.5 cubic centimeter increments.

FIG. 8. Cystometrograms of dog 12. a, Two weeks after the mesenteric pedicle to the reconstructed bladder was severed; capacity 35 cubic centimeters; residual urine and incontinence. b, Three months following second reconstruction, capacity 75 cubic centimeters; no residual urine, or incontinence. Filling increments 12.5 cubic centimeters.

through the vagus nerve; this suggests the possibility that neural communications with the centers controlling micturition may have been re-established through association tracts. The plausibility of this explanation is suggested by the numerous conditioned response experiments involving the autonomic nervous system described by Pavlov and others.

Thus, taken separately, tissue by tissue, most of the phenomena occasioned by the transplanted intestinal grafts may be accounted for on the basis of physiologic adaptations. When considered as a whole, however, the functional restitution of the denervated bladder might properly be regarded as a transference of function in the transplanted graft. That such a complex function as normal micturition, with all its physiologic, psychologic, and sociologic implications, could be accomplished through transplanted intestinal tissue was wholly unexpected, especially since transference of function has not previously been demonstrated within the central nervous system in mammals.

The clinical implications of this study are self-evident. Replacement of the bladder surgically excised for neoplasm or other disease, repair of exstrophy or other anomalies, and reconstruction of the functionally deranged or neurogenic bladder should be in accord with sound physiologic principles. When the urinary stream is diverted into the gastrointestinal tract, there is reabsorption of fluids, electrolytes, and nitrogenous wastes, and frequently ascending infection and stricture at the anastomotic sites. When segments of the intestinal tract with their intact mucous membrane are used to replace the bladder, the same dire complications arise. The bladder is so comprised that minor functional aberrations are rather readily manifest in pathologic conditions; with limited capacity of the bladder, frequency of urination occurs, and, with incomplete emptying, residual urine is found and with it the inevitable infection that stasis implies. It is not sufficient to replace the bladder with a structure which grossly resembles the original organ, there must be functional restitution as well.

A technique for bladder reconstruction which would approximate the normal gross and microscopic appearance of the bladder as well as simulate the functional capacities of the organ would be invaluable.

SUMMARY AND CONCLUSIONS

1. The micturition patterns and cystometry in a series of dogs whose bladders were reconstructed with reversed seromuscular ileal grafts were studied and compared with those in a series of intact animals.

2. Stimulation of the vagus nerve in the normal animal elicited no change in intra-

vesical pressure, while stimulation of the pelvic nerves produced a prompt visible contraction of the detrusor muscle with increase in the intravesical pressure.

3. Stimulation of the vagus nerve in dogs with reconstructed ileal bladders was found to produce a pronounced rise in intravesical pressure.

4. Stimulation of the pelvic nerves in dogs with reconstructed ileal bladders was found to have no demonstrable effect on the intravesical pressure, indicating the absence of regeneration of the sacral parasympathetic fibers into the graft during the period of observation.

5. Neurogenic bladders were produced in dogs by 4 types of neurologic lesions: pelvic neurectomy, dorsal rhizotomy, cauda equina section, and spinal cord transection.

6. These 4 types of denervated bladders were reconstructed with reversed seromuscular ileal grafts; observations on these animals from 1 to 6 months postoperatively revealed continence, a normal micturition pattern, no significant residual urine after voiding, and essentially normal cystometry.

7. The maximum biologic capacity of smooth muscle may best be ascertained by transplantation where there is altered environment and an increased physiologic demand.

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PREVENTION AND PRODUCTION OF THROMBOSIS BY ALTERATIONS IN ELECTRIC ENVIRONMENT

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THE RELATIONSHIPS between injury, electric potential across a blood vessel wall, and thrombosis have been investigated by Sawyer and Pate (2, 3, 4). The normal stat potential difference between the adventitia and intima, or blood within the vessel, was demonstrated to be 1 to 5 millivolts with the blood or intima relatively negative in respect to the adventitia. Injury altered the normal potential difference, and when the polarity was reversed, making the blood or intima relatively positive in respect to the adventitia, thrombosis frequently occurred. Red blood cells, white blood cells, and the protein components of blood have negatively charged surfaces at the normal *p*H of blood, and, in vitro, currents in the milliampere and microampere range precipitate a thrombus on the positive electrode. Passage of electric current to reverse polarity in a segment of blood vessel wall resulted in thrombosis under the positive electrode. The present study constitutes a further investigation of the bioelectric phenomena associated with intravascular thrombosis.

METHODS AND RESULTS

Electric production of thrombi. In the first group of experiments, the effect of a positive current on a segment of blood vessel was investigated. A 6 centimeter segment of superficial femoral vein was isolated in nembutal anesthetized dogs, and the vessel was occluded proximally by means of a silk ligature. A 3 centimeter segment was loosely encompassed by a thin platinum sheath, and another platinum wire was inserted into the ipsilateral leg muscle. The platinum sheath and wire were connected to a rheostat, and two 4½ volt, dry cell batteries were placed in series so that a current flowed across the vessel-muscle circuit with a vascular-sheath electrode as a positive pole (Fig. 1). Five dogs were studied, and a current of 5 milliampere magnitude with the vascular positive was maintained for a 1 hour experimental period. The opposite leg was used as a control, and the preparation consisted of proximal occlusion by means of a silk ligature and encompassing a 3 centimeter segment of vessel by means of identical thin platinum sheaths.

At the end of the 1 hour experimental period in all 5 vessels which had received a milliampere current, thrombi formed (Fig. 2). Microscopic examination revealed no destruction of the blood vessel wall, and histologically the thrombi were identical to thrombin induced clots of spontaneous thrombin. In 4 control limbs with the same mechanical preparation, but without the imposition of a positive current, no thrombi formed during the 1 hour experimental period (Table I).

Effects of heparin and dicumarol. In the 4 dogs given dicumarol, the prothrombin time was reduced to less than 30 per cent of the normal control as measured by a modified one stage test. The superficial femoral vein was then subjected to a 5 milliampere positive current as previously described. At the

TABLE I.—PRODUCTION OF THROMBUS

	No. of experiments	*Thrombosis*	*No thrombosis*
Control	4	0	4
5 milliamperes, 1 hour	5	5	0
Dicumarol, 5 milliamperes, 1 hour	4	4	0
Heparin 5 milliamperes, 1 hour	4	0	4

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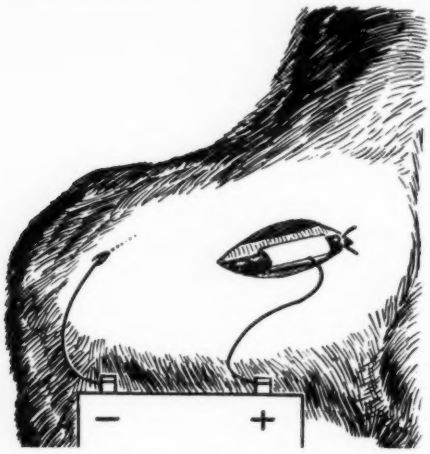

FIG. 1. Method of imposing a 5 milliampere, 9 volt, positive current on a segment of blood vessel.

end of 1 hour, the vein was opened and inspected for thrombi. In each of the 4 vessels studied, significantly large thrombi formed.

Four animals received aqueous heparin in sufficient quantities to increase the clotting time, as performed by the Lee White technique, to well over 30 minutes, and then 5 milliamperes of positive current were imposed upon the superficial femoral vein in a similar fashion. After a 1 hour experimental period, the veins were opened and in none of the animals was a thrombus evident (Fig. 3).

Under nembutal anesthesia, a laparotomy was performed; and a platinum electrode, the tip of which was exposed and the remainder insulated with polyethylene, was threaded up the abdominal aorta by means of the middle sacral artery. A 1 centimeter square platinum electrode was sutured to the adventitia at a point opposite the tip of the internal electrode. By means of a potentiometer, stat potential differences between the adventitia and blood within the vessel were measured. Ten cubic centimeters of saline, followed by 10 milligrams of aqueous heparin diluted to 10 cubic centimeters with saline, were injected into the saphenous vein. Stat potential differences were measured at 5 minute intervals for a half hour, and clotting times were also checked.

Saline infusion did not significantly alter the potential difference between the adventitia of the aorta and the flowing blood, and there was no change noted in the clotting time. Heparin rapidly increased the electronegativity of the blood in respect to the adventitia by 105, 125, and 160 per cent in the 3 dogs studied. Clotting times increased to over 3 hours in these animals after heparinization.

Subsequent injection of protamine sulfate in amounts equivalent to the heparin administered resulted in the return of potential difference to the control level and a con-

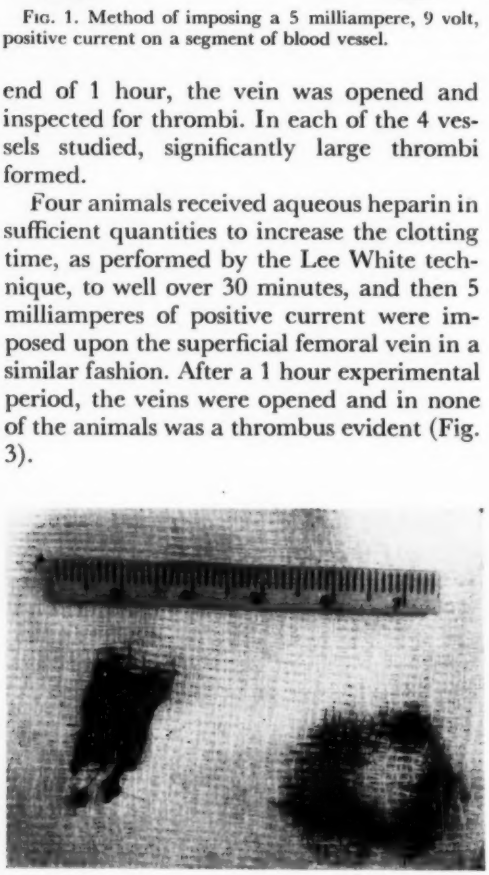

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FIG. 2.

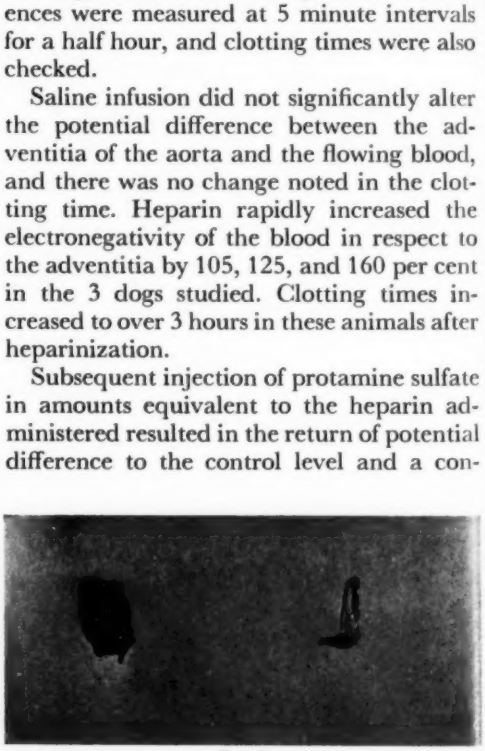

FIG. 3.

FIG. 2. a, Production of thrombus with 5 milliampere positive current for 1 hour. b, Control, no thrombus.

FIG. 3. Heparin protection: a, left, Thrombus is seen on intima of vessel after 5 milliampere positive current of 1 hour. b, right, Intima is clear, no thrombus in heparinized (5 mgm.) animal with 5 milliampere positive current to vessel segment.

comitant return of clotting time to that of the control in each of the 3 dogs studied.

Electric protection against thrombosis. A 4 centimeter segment of superficial femoral vein was isolated bilaterally in nembutal anesthetized dogs. On one side, this segment was encompassed by a thin platinum sheath, and a platinum wire was inserted into the leg muscle. A circuit was established with a dry cell battery so that current in the 1 to 5 milliampere range flowed in direction to increase the electronegativity of this segment of the blood vessel. Using the method described by Holden and others for production of a thrombus, 500 units of topical thrombin in 0.5 cubic centimeter of saline were injected bilaterally via a tributary vein into the segment of femoral veins, which have been occluded proximally. After 30 minutes, distal noncrushing clamps were applied, the veins opened, and thrombi extracted. The opposite leg was used as a currentless control, with the same mechanical features of proximal occlusion—placement of a platinum sheath around a segment of superficial femoral vein; injection of 500 units of topical thrombin, but without the imposition of an electrically negative current upon the blood vessel (Fig. 4).

In the 20 dogs studied, a thrombus the size of the occluded vessel was extracted from the currentless control vein. In 14 animals, there was no thrombus in the electrically "protected" veins; in 4 there were minute thrombi, which were significantly smaller than their respective controls; and in 2 animals large thrombi had formed.

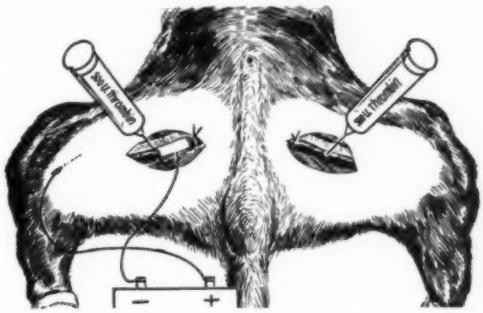

FIG. 4. Preparation to test protection of negative current (1 to 5 milliamperes, 9 volts) against thrombin induced thrombosis.

DISCUSSION

The association between bioelectric alterations and intravascular thrombosis has been demonstrated. An electrically positive environment favors the formation of a thrombus and an electrically negative environment protects against the standard method of induced thrombosis. The summation of these results suggests that an electric alteration is one of the common denominators for intravascular thrombosis, which occur after blood vessel trauma and changes in the constituents of blood.

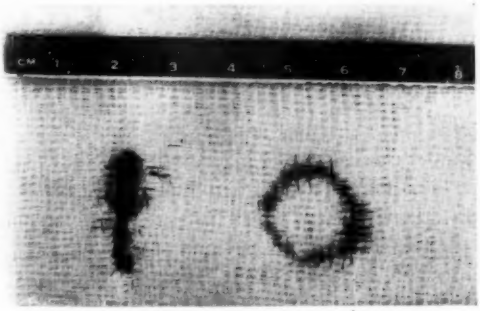

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FIG. 5. Electric protection against thrombosis (2 milliamperes): a, Clot extracted from control vessel. b, Absence of thrombosis in segment with induced electronegativity.

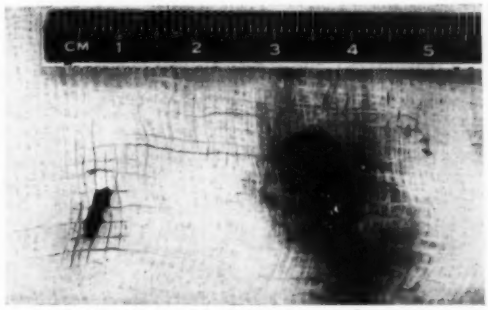

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FIG. 6. Electric protection against thrombosis (4 milliamperes negative): a, Minimal thrombus in electrically negative segment. b, Thrombus extracted from currentless control.

It is suggested, that in view of the structure of heparin, in which the amino group is acetylated and therefore nonreactive, its anticoagulant properties are the result of a physical-chemical reaction. It has a high molecular weight and carries an exceptionally strong negative charge, apparently the strongest of all organic components of the animal body. It is probable that heparin effectiveness is, in part, related to physical-chemical reactions and is considered superior to dicumarol and related drugs as the treatment for a broad spectrum of venous thrombosis.

SUMMARY

1. The imposition of 5 milliamperes of positive current upon a segment of superficial femoral vein which has been occluded proximally results in thrombosis after 1 hour.

2. Heparin protects against this electrically induced thrombosis while dicumarol has no effect.

3. Injection of heparin increases the electronegativity of flowing blood in respect to the adventitia of a blood vessel, concomitant to its increase in clotting time.

4. The imposition of an electrically negative current upon a segment of blood vessel protects against a standard method of thrombosis.

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THE TREATMENT OF PAROSTEAL OSTEOMA OF BONE

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PAROSTEAL OSTEOMA occurs in both benign and malignant forms, with the malignant form a predominant feature of the disease. In 1951 the authors (6) reported 16 cases as a new entity, histologically similar to myositis ossificans, but with a more intimate relationship to bone and having a graver prognosis. Jaffe and Selin as well as Coley and Higinbotham, have briefly described a type of osteogenic sarcoma which has the features of the disease described in this report. More recently Dwinnell, Dahlin, and Ghormley and Dahlin have written on this subject, preferring to designate the disease entity as "parosteal osteogenic sarcoma," thus emphasizing the growth potential or subsequent malignant changes noted in many of the cases studied. These authors reported 15 cases.

The relationship of the malignant phase of parosteal osteoma to a preceding benign growth appears to be an unusually intimate one. The initial lesion is most frequently a benign proliferation of ossifying fibrous tissue, which results in a rounded bony mass projecting from the shaft of a long bone at or near the metaphyseal region. There is usually no base or pedicle of orderly bone growth, formed by the underlying normal bone and capped by cartilaginous tissue, as is often seen in osteochondromas or exostoses. Instead, the ossifying mass, by contiguity, eventually invades adjacent cortical and cancellous tissues at one or more points. The process also extends in an outward direction into the soft parts, often involving the muscles with or without a periosteal pseudoencapsulating membrane. Islands of cartilage may be found within the ossifying mass, intermingled with more direct ossification from fibrous tissue. The cartilage does not form a separate zone of superimposed tissue, such as occurs in osteochondromas. It would appear, therefore, that the benign phase of the tumor is characterized by ossifying fibrous tissue arising in the region of the periosteum of long bones—femur, tibia, fibula, humerus, ulna, and radius. The tumor shows a tendency to progressive growth and to ultimate malignant change. The malignant phase of the process is akin, in its histology, to sclerosing osteogenic or fibrosarcoma. The evolution from benign to malignant forms often appears to be a gradual process extending over a number of years. The number of 5 year cures (60 per cent) obtained in this group by resection or amputation is unusually high, as compared with rates of survival among many other forms of bone sarcoma.

The authors have previously suggested that the source of the new bone in parosteal osteomas was from bands of skeletal blastema, displaced from primitive periosteum. In support of this possibility are the points of predilection at the surfaces of long bones relatively free of muscular attachments where, it may be surmised, there is a lack of differentiating influence of stress and strain.

CLINICAL FEATURES

Parosteal osteomas occur most often in the first 4 decades of life, between the ages of 8 and 40 years (Fig. 1). In 10 of 22 cases (Table I) which we are reporting, the lesions were found on the posterior surface of the lower femur, bulging into the region

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TABLE I.—SUMMARY OF 22 CASES OF PAROSTEAL OSTEOMA

Case No. *Sex* *Age, yrs.*	*Duration*	*Location*	*Pathology at last operation*	*Treatment*	*Result*	*Well*
1 F 26	7 yrs.	Lower femur	Malignant	Excision 5-7-09 (benign); excision Jan. 1912; amputation April 1912	Dead 1-12-13, met. after 7 mos.	
2 F 34	4 mos.	Upper fibula	Malignant	Resection Oct. 1919 (benign); recurrence 1922 (benign); amputation Feb. 1925	Well 1932	7 yrs.
3 M 28	1 yr.	Upper humerus	Malignant	Excision Feb. 1924; radium; amputation Sept. 1924	Dead Oct. 1929, met. after 5 yrs.	
4 M 18	2.5 yrs.	Lower femur	Malignant	Amputation 1929	Suicide 1932, after 3 yrs.	
5 F 32	2 yrs.	Lower femur	Malignant	Excision Feb. 1921	Dead March 1930, met. after 9 yrs.	
6 F 28	3 yrs.	Lower femur	Malignant	Excision 1934 (benign); 1935 (benign); 1937	Lost	
7 M 23	18 mos.	Upper humerus	Malignant	Resection 1940	Well 1944, lost after 4 yrs.	
8 M 27	7 yrs.	Lower femur	Malignant	Amputation Oct. 1944	Well Oct. 1949	5 yrs.
9 M 36	6 wks.	Lower femur	Malignant	Biopsy, amputation Oct. 1945	Well Oct. 1950, lost trace	5 yrs.
10 F 33	19 mos.	Lower femur	Benign	Excision July 1948 (benign); 10-12-53 amputation	Well March 1958	5 yrs.
11 F 25	6 mos.	Lower femur	Benign	Excision 3-15-46; irradiation	Well April 1958	12 yrs.
12 M 10	3 mos.	Lower femur	Benign but cellular	Excision 10-5-42 (benign); amputation Jan. 1946	Died Jan. 1950, met. after 4 yrs.	
13 M 56	5 mos.	Upper ulna	Malignant	Excision 7-5-47 (benign); biopsy 5-16-49; resection upper ulna 6-6-50; amputation 9-4-50	Dead 1951	
14 F 10	2 mos.	Lower humerus	Malignant	Resection 7-10-25	Last reported well 1940	15 yrs.
15 M 21	1 mo.	Upper fibula	Malignant	Resection 8-3-48 (benign); biopsy for recurrence 1-9-50	Died 1-28-51 with met.	
16 M 27	2.5 yrs.	Lower femur	Malignant	Biopsy 8-13-49; excision, 9-13-49; amputation, 10-10-49	Died 7-26-55 with met.	
17 M 33	5 wks.	Upper humerus	Benign	Mild radiation Dec. 1935; excision 4-15-37	Well 3-28-58	23 yrs.
18 F 8	2 mos.	Upper radius and ulna	Malignant	Excision Sept. 1944 (benign); recurrence, excision Feb. 1945	Well Jan. 1958	14 yrs.
19 F 18	5 wks.	Upper tibia	Benign but cellular	Resection of tumor 11-4-33 followed by amputation left leg in few months	Well 3-19-58	25 yrs.
20 F 14	1 yr.	Lower tibia	Benign	Biopsy 12-27-49; excision 1-18-50	Well 10-23-57	7 yrs.
21 F 25	1 yr.	Lower femur	Malignant	Biopsy 8-18-39; amputation left thigh between upper and lower third 8-25-39	Well 4-1-58	19 yrs.
22 F 30	1 wk.	Upper femur	Benign but cellular	Excision 10-11-54	Well 3-29-58	3+ yrs.

of the popliteal space. Similar growths were observed about the upper femur, the upper and lower portions of the humerus, the upper ulna and radius, the upper fibula, and lower tibial regions (Fig. 2). There were 12 females and 10 males among the patients studied.

A swelling or mass and local pain or tenderness were the outstanding clinical features. The duration of symptoms extended over a period of weeks to years. Ten of the patients had noticed a mass for 1 year or more. One patient had noticed an increasing enlargement of her lower thigh for 7 years. At times, progressive increase in the size of the mass was the only symptom. Apparently, trauma had not played a significant role in the development of these lesions, although in 3 patients it led to the discovery of the mass. In 1 patient, irradiation for skin disease preceded the bone lesion by 32 years.

On examination, a mass of bony hardness is felt, which is firmly attached to the adjacent bone. The tumor extends into the soft parts and may involve muscle. The periphery of the bony mass is usually smooth in contour, although in a few cases it was found to be infiltrating. The slow growth of the tumor, its discrete character, and the normal appearance of the overlying soft parts suggest a relatively benign growth.

There are no systemic features, such as the leucocytosis and fever frequently seen in rapidly growing sarcoma of bone.

ROENTGENOGRAPHIC FEATURES

In the roentgenogram the tumor is seen as a parosteal mass of ossifying tissue which involves the ends of long bones but has its most prominent manifestations in the overlying soft parts (Fig. 4a and b). The tumor, in its early phases, is visible as a dense, irregular or rounded mass of new bone which is firmly attached to the cortex along a portion of its broad base, but is separated for most of its circumference from the underlying skeletal structures (Figs. 5, 6, 7, and 8). There may be several discrete smaller

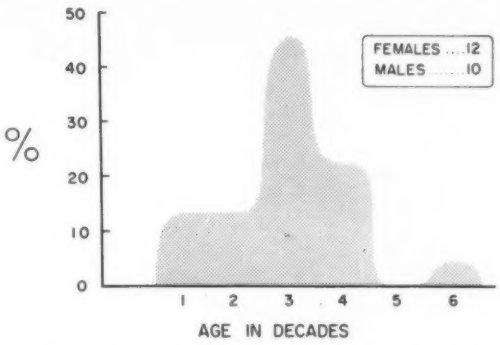

FIG. 1. Parosteal osteoma occurring most often in the first 4 decades of life. The male and female sex distribution is not significantly different.

masses. This is particularly true if recurrence has followed a previous operation. The underlying bone forms an irregular sclerosis, suggesting a platform for the new growth through widening of the cortex and

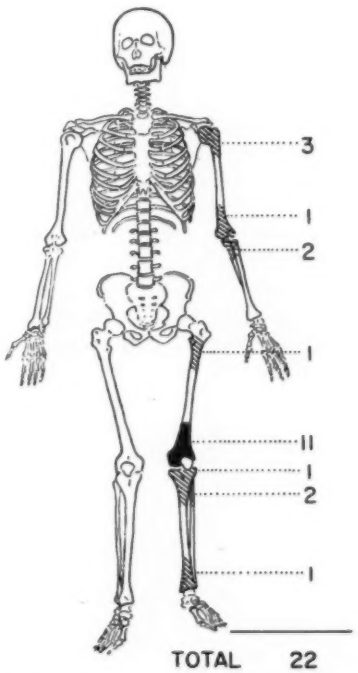

FIG. 2. Skeletal distribution of parosteal osteoma. Note the preponderance of lesions in the posterior metaphysial region of the lower femur.

FIG. 3. Gross appearance of parosteal osteoma (Case 10).

with some periosteal reaction. In late cases, the densely ossifying mass seems to envelop the underlying bone. In recurrent tumors, following surgical excision, often after prolonged intervals, active and prominent medullary involvement may be seen, with obvious roentgenographic features of malignant change. In view of the density of the osseous shadow and its size in primary cases, there is surprisingly little destruction or reaction in the adjacent bone. The diagnostic features of primary lesions are the density of the osseous mass, well delineated margins along one or more aspects of the periphery, and the occasional independent or discrete secondary osseous growths.

GROSS AND MICROSCOPIC FEATURES

A seemingly well encapsulated bony mass is usually found at operation (Fig. 3). It frequently displaces the muscular structures, but occasionally invades the muscle bundles. Dissection shows that the mass is attached to the underlying bone. The tumor is often attached to the periosteum but can be removed from the periosteal surface. Occasionally it is necessary to remove a portion of both periosteum and cortex because of underlying bone involvement. The bone invasion may be characterized as sclerosis or erosion. The consistency of the tumor varies from fibrous tissue, undergoing partial calcification, to that of cancellous bone. Radiating bony trabeculae are seen on cross-section, traversing coarse fibrous tissue. Irregular concentric masses of cancellous bone may be found in the gritty fibrous substance of the matrix. Small discrete osseous masses can be found separated from the main growth.

The microscopic features of parosteal osteoma embrace the aspects of spongy osteoma, ossifying fibroma, cellular fibroma, or low grade fibrosarcoma. A variety of forms of osteogenesis are disclosed (Fig. 5c, d, e, and f). Many well formed, regularly arranged osseous spicules (trabeculae) are noted. These are surrounded, usually, by a single layer of osteoblasts. The intervening tissue may undergo sclerosis and hyalinization, or persist as atypical proliferating spindle cells. At the periphery the growths are more apt to show increased cellularity and, occasionally, the features of osteogenic or fibrospindle cell sarcoma (Fig. 9a, b, c, and d). Islands of normal or atypical cellular cartilage proliferation may be seen in the tumors. Evidence of malignant change is sometimes restricted to small foci, thus requiring a careful and thorough survey by the pathologist for accurate appraisal. The recurrent tumors may reveal an increase in atypical cellular forms, with an accompanying increased growth potential.

PROGNOSIS AND TREATMENT

A review of the 16 cases previously reported by the authors (6), with the addition of 6 new cases, emphasizes the fact that parosteal osteomas are potentially malignant lesions. At the initial operation, the specimen often may be chiseled away or resected with a portion of the underlying bone, and fail to show histologically malignant features on adequate examination.

Of the 22 cases studied, the original lesion appeared to be benign in 14 patients. Subsequent surgery, necessary for recrudescence of disease, revealed the tumor as benign in

only 2 cases at the second operation. The tissue removed in the only or final operation was considered malignant in 15 patients, benign but cellular in 3 specimens, and typically benign in 4 instances.

The history of slow growth, the circumscribed character of the neoplasm at operation, and the benign histology of the excised mass may give the operator a false sense of security. The temptation is to consider these growths as atypical examples of myositis ossificans. The subsequent course of the disease, however, compels re-evaluation. The irregular osseous surface of the cortex at the operative site, showing renewed or continued activity, presages the development of masses of irregular bone which penetrate into the adjacent soft parts. Eventually, the recurrent mass tends to surround and invade the bone in frankly sarcomatous fashion.

From the standpoint of prognosis, 4 of the 22 cases are considered indeterminate (Cases 4, 6, 7, and 22).

Among the 18 determinate case reports, 11 patients are living and well 5 or more years following resection (excision) or amputation. Eight of these patients are living and well for from 7 to 25 years following treatment. Three additional patients lived 5 or more years (Cases 3, 5, and 16) and then died of metastases. One woman with femoral parosteal osteoma lived 9 years after excision and then died of metastases. Four patients died of their disease from 7 months to 4 years after definitive surgery was carried out (Cases 1, 12, 13, and 15). The absolute 5 year survival rate proved to be 63.6 per cent, while the adjusted 5 year survival rate was 60 per cent in the patients treated. This latter rate does not include the indeterminate cases nor the patients who lived 5 years and subsequently died of their disease. Of those patients surviving 5 years or more without disease, the final operation was amputation in 6 cases and excision or resection in 5. Two of the latter patients received x-ray therapy in addition to the local removal of the tumor.

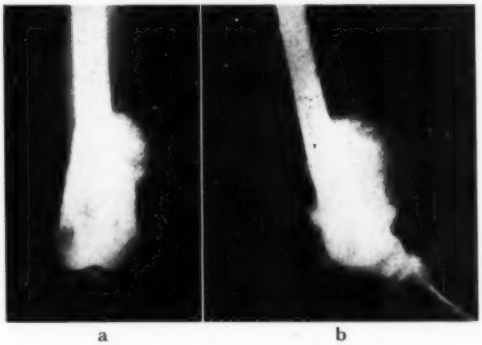

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FIG. 4. Case 5. a and b, Roentgenograms of a parosteal osteoma of lower femur which was resected and then recurred. Patient refused further operation and died 9 years later.

The indolent behavior of the disease is illustrated by a patient 25 years old, a girl (Case 11) who noticed soreness above the right popliteal space of 8 months' duration. Roentgenograms showed a circumscribed, osseous mass which was posterior and medial to the lower end of the femur and about 7 centimeters in diameter (Fig. 6a and b). The underlying femoral bone seemed to form an irregular platform for this mass. In March 1946, an encapsulated bony tumor was excised, which was separated with some difficulty from the underlying periosteum. Pathologic examination showed benign new bone formation and proliferating fibrous tissue without evidence of malignancy (Fig. 6c and d). Following operation, the femoral periosteum became progressively more elevated and an area of rarefaction appeared in the cortex of the femur. The region was treated by repeated roentgen therapy totaling 3,000 roentgens. In the subsequent years the femur has been examined every 6 months roentgenographically. There has been no further change, and the patient has remained symptom-free (April 1958).

Another patient (Case 1) with an apparently indolent disease had noted a mass about the outer condyle of her left lower femur for 7 years. Two excisions were then carried out 2 years apart and, finally, an

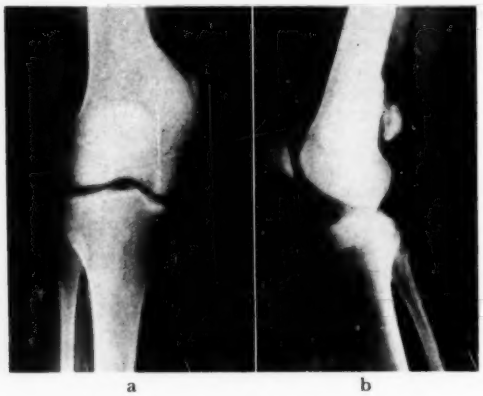

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FIG. 5. Case 9. a and b, Roentgenograms of a parosteal osteoma of the lower femur treated by primary amputation. The patient is living without disease after 5 years. c and d, Photomicrographs showing the central osseous portion of tumor with area of cartilaginous proliferation. e, Photomicrograph showing proliferating margin of tumor with bony spicule formation. f, Photomicrograph showing fully developed fibrosarcoma.

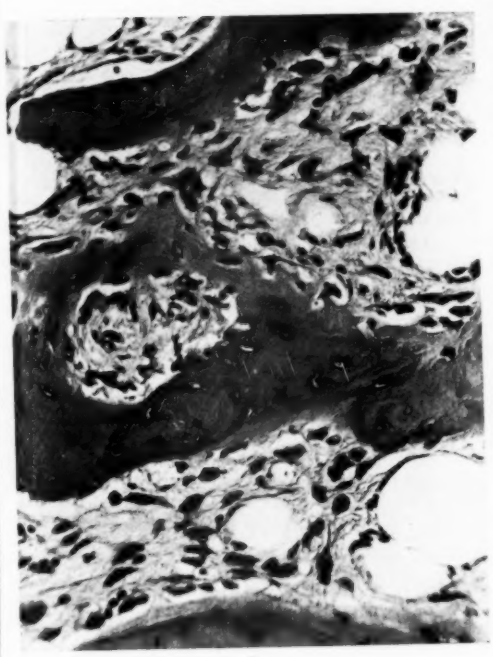
amputation was performed 4 months later but, after 7 months, the patient died of disease.

On the other hand, a patient (Case 15) had noted a lesion in the left upper fibular region for only 1 month. A resection of the upper part of the fibula was carried out. Seventeen months later recurrence was suspected. A biopsy revealed disease, but further surgery was declined. The patient died 1 year later with metastases. Such rapid progression of the disease illustrates the ultimate potential of the disease process.

Survival is not completely related to the growth potential, however, but also to the adequacy of the tumor ablation. Some patients are living and well after 5 years, having had a relatively short duration of symptoms, and with only local excision as the definitive treatment. The host-tumor relationship appears to be quite variable in these patients but suggests that we are dealing with a potentially malignant lesion. At the first operation the tumor was found to be malignant in only 8 of 22 cases, hence we prefer to call the lesion "parosteal osteoma," rather than "parosteal osteogenic sarcoma."

A decision regarding the proper type of treatment must be based on a careful study of the therapy used and the results obtained. In the determinate cases, treated only by excision or resection of the tumor with or without irradiation, 5 patients are living 5 years free of disease; 2 patients are dead. In 8 other cases, with excision or resection of the tumor as the primary treatment, recrudescence of the disease followed in from a few months to 6 years and resulted in amputation. Three of these patients are living and well after 5 or more years, while 5 individuals died of their disease. One of the living patients had a tumor with histopathologic changes of benign but cellular type. The referring pathologist and surgeon ultimately preferred to carry out amputation (Case 19). Three patients had primary amputation for tumors with malignant changes and all are living after 5 or more years without disease. X-ray therapy appeared to be effective in only 1 patient.

We cannot discount the experience of those reporting similar cases in the literature. Dwinnell, Dahlin, and Ghormley, in reporting 15 such cases, indicate that 5 patients are dead (3 from known metastatic disease); 9 patients appear well without evidence of tumor. Six of these patients have had amputation; 1 has had resection of the distal third of the involved bone, and 1 has had local excision and roentgen therapy. Of 1 of these cases they state, "we cannot satisfy our criteria for malignancy." They believe that the "lesion (parosteal osteogenic sarcoma) is malignant from its inception." Dwinnell and associates state, "there is no evidence from this series that the tumor arises in some pre-existing benign lesion."



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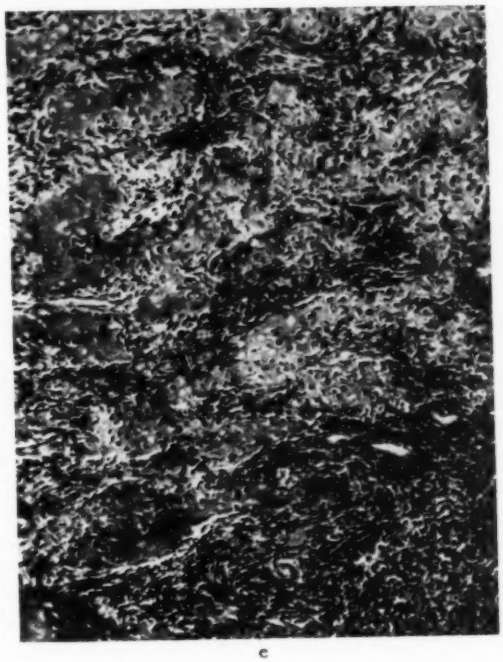

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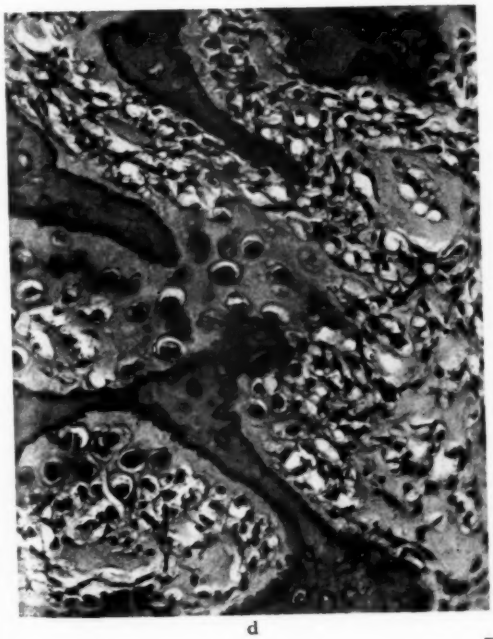

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FIG. 5.

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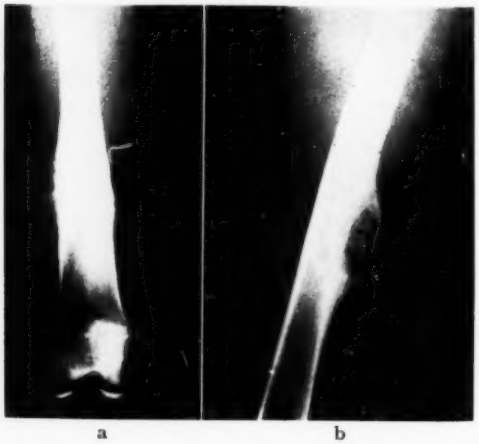

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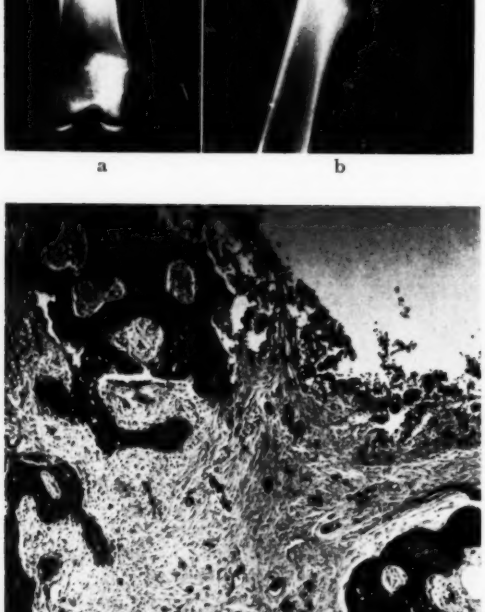

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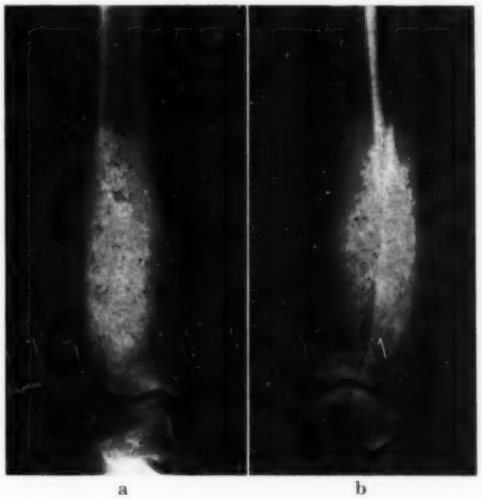
FIG. 6. Case 11. a and b, Roentgenograms of parosteal osteoma of femur treated by excision in March 1946, postoperative x-ray therapy; well April 1958. c, Photomicrograph showing relatively inactive osseous and fibrous tissue. d, Cellular fibrospindle cell proliferation with active osteogenesis.

They believe the lesion to be a form of osteogenic sarcoma, but that it differs markedly from the ordinary osteogenic sarcoma which has a high degree of malignant potential and almost always involves the medulla.

Bradley Coley, in a personal communication after reviewing our original paper, stated, "I was very much interested in your paper. . . . We have encountered cases that appear to us to be similar to this and have noted, as you have, that they are potentially serious cases with a definite tendency to malignant transformation."

We must again reiterate, although the total number of cases available for study are few (22 patients among 2,000 primary bone tumors), that our follow-up studies and

reports by others indicate that we are dealing with a slowly evolving malignant neoplasm. It would further appear that the best results are to be obtained by amputation. Inability to confirm the malignant nature of the growth histologically following excision imposes a serious responsibility upon the surgeon and pathologist. Suffice it to say that bold, early, ablative surgery by resection or amputation will cure more cases than temporizing surgical excisions. If complete resection of relatively inactive tumors can be accomplished, cure should result. If there is any question about adequate en bloc resection, amputation is indicated. A factor to be considered in contemplating the conservative excision of some of these tumors is the increased malignant potential which is manifested in the recrudescence of the disease. When pathologic changes show frank sarcoma, amputation is indicated at once. Such pathologic conformation is usually easily found in large growths, either in a primary lesion or in recrudescent growth.



a b

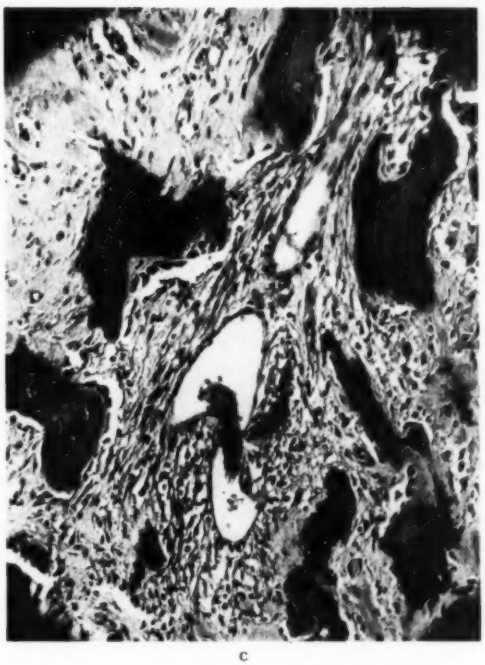


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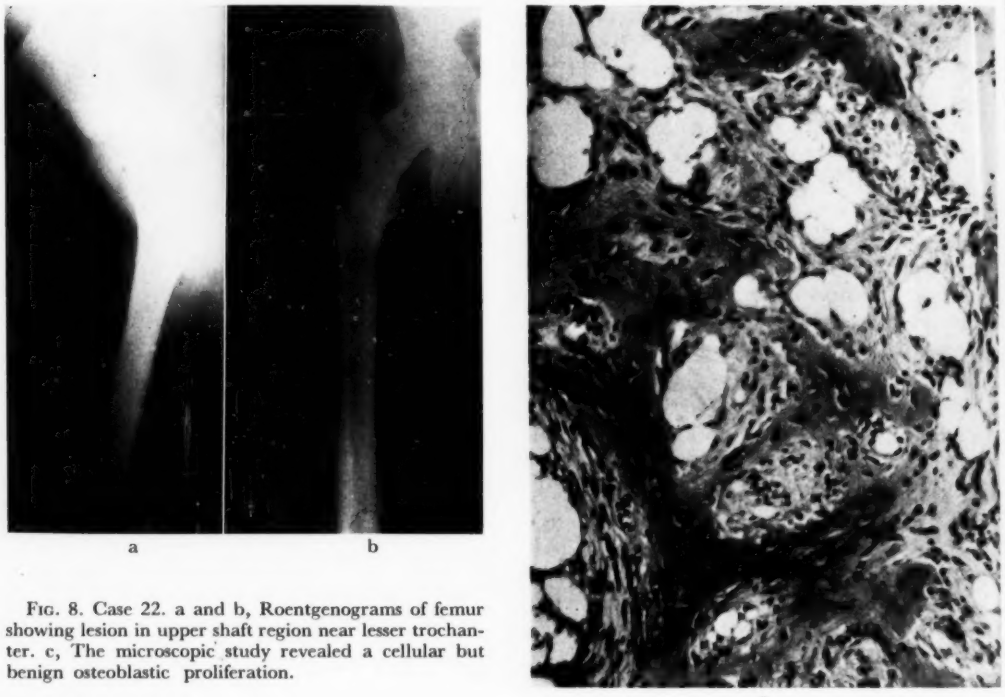
FIG. 7. Case 20. a and b, Roentgenograms showing parosteal osteoma at lower end of tibia. Note the overlay of the dense sclerotic shadow which upon, c, microscopic examination reveals a benign proliferation of osteoid spicules in a bed of vascular fibrous tissue. Following excision, this patient has remained well after a period of 7 years.

DIFFERENTIAL DIAGNOSIS

Parosteal osteoma must be differentiated from other conditions such as: (1) localized myositis ossificans; (2) intraligamentous osteoma or osteoma of the tendon sheath; (3) sclerosing osteogenic sarcoma; and (4) osteochondromas and exostoses.

Localized myositis ossificans gives a definite history of trauma in 60 per cent of the cases. The swelling reaches its maximum in 6 to 12 weeks and, thereafter, remains stationary. The roentgenogram shows a laminated triangular shadow paralleling the long bone, following the fascial planes of the muscle. The ossification is separated from the underlying bone in 1 or more views, and the underlying bone is unaffected. The histologic structure is variable. Bone is formed directly from connective tissue and also via cartilage, and there may be zones of bone resorption with giant cell osteoclasts. Circumscribed myositis ossificans is practically always a benign lesion. In cases in



a b c

FIG. 8. Case 22. a and b, Roentgenograms of femur showing lesion in upper shaft region near lesser trochanter. c, The microscopic study revealed a cellular but benign osteoblastic proliferation.

which malignancy has supervened, as in the case reported by Pack, the histology is that of frank sarcoma. Most of the cases reported as malignant transformation in myositis ossificans—and the cases are few—are probably examples of parosteal osteoma, as reported by Coley, Chambers, and Paul.

In parosteal osteoma the duration of symptoms is usually in months and years, rather than weeks. The ossifying mass is pseudocircumscribed or infiltrating, and grows progressively in size. The underlying bone shows widening with cortical thickening and periosteal reaction. Histologically, the ossification is usually directly from fibrous tissue, and cartilaginous foci are less common.

Intraligamentous osteomas or osteomas of the tendon sheath are sometimes referred to as sesamoidomas. These are benign encapsulated osteomas embedded in tendon sheaths or ligaments. We have seen 1 case in the quadriceps tendon below the patella, 2 in the Achilles tendon above the os calcis, and the remainder of 10 cases have been in the tendon sheaths about the hand and foot. They are apparently congenital supernumerary sesamoid bones and do not show the progressive growth or cellular fibrous areas found in the parosteal osteomas under discussion. Sesamoidomas do not approach parosteal osteomas in size.

Sclerosing osteogenic sarcoma begins within the bones. The focus of origin is subcortical, although late in the disease much periosteal new bone of malignant character may be formed. Except in the zones of periosteal lipping, where reactive new bone of benign character may be found along with sarcoma, the tumor is composed entirely of irregular osteoid spicules without definite arrangement, intermingled with a disorderly profusion of malignant osteoblasts and fibroblasts. Sclerosing osteogenic sarcoma has a rapid clinical course. The prolonged slow growth, extending over years, seen in

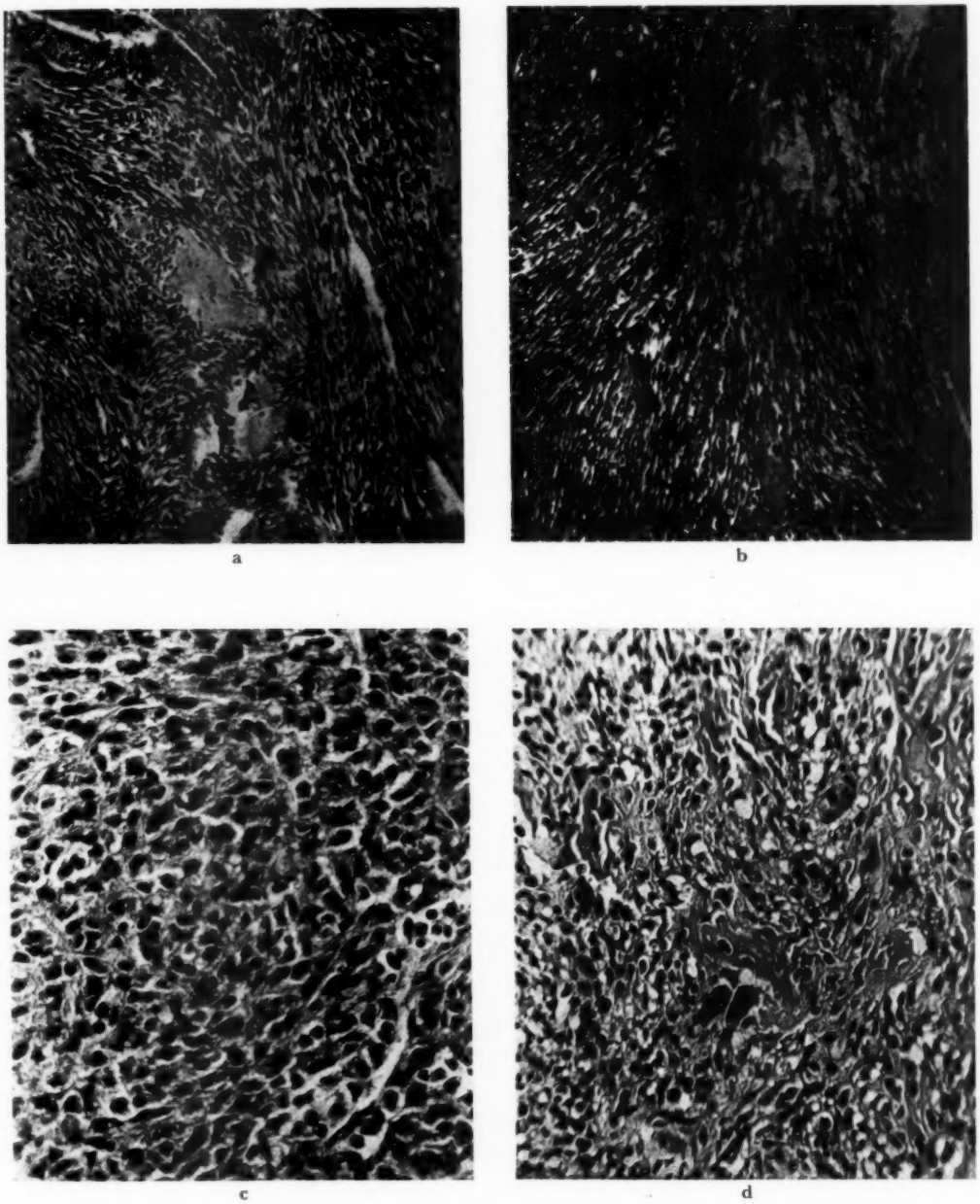


FIG. 9. Photomicrographs of malignant transformation which often takes place in parosteal osteoma following recrudescence after temporizing surgery (repeated incomplete resection or excision). a, Marked cellularity of fibro-osseous tissue with atypical cell morphology (Case 3). b, Fibrosarcoma with abortive bone formation (Case 3). c, Cellular proliferation of malignant osteoblastic tissue much like that seen in osteolytic osteogenic sarcoma (Case 15). d, Fully developed sclerosing osteogenic sarcoma (Case 15).

parosteal osteoma, is not characteristic of these highly malignant new growths.

Osteochondromas and exostoses in some instances have a broad base, lending a superficial resemblance roentgenographically to parosteal osteoma. The stalk or base, however, is continuous with the cortex of the normal bone. The periosteal covering is intact and, most often, the cartilage is present in the form of a cap over the peripheral portion of the lesion. Chondrosarcoma occasionally arises in osteochondroma (8 per cent).

CONCLUSIONS

Twenty-two cases have been reported of a new entity in bone tumors, histologically similar to myositis ossificans, but with a more intimate relation to bone and a graver prognosis. This neoplasm, termed by us as "parosteal osteoma," occurs in both benign and malignant forms, with the malignant form predominating. The tumor occurs most frequently in the first 4 decades of life (Fig. 1), principally on the posterior surface of the lower femur (Fig. 2), and produces symptoms of tenderness or limitation of motion. On roentgen examination, a mass 5 to 10 centimeters in diameter, densely ossified, circumscribed, frequently sharply outlined, and occurring outside the bone but contiguous with it, is usually visible. At operation, the mass is fused with the periosteum, with pseudoencapsulation often seen at its outer margins. Grossly, on section, the tumor has a firm, dry, striated surface much like fibrosed cancellous bone. Microscopically, although adult bone and fibrous tissue predominate, foci of cartilage cells may be seen. At the periphery the growths are more apt to show increased cellularity and, in a number of cases, have shown features of fibrospindle cell sarcoma. Following incomplete excision of supposedly benign growths, roentgenograms at intervals may show evidence of growth potential or definite features of malignant change. Of 18 determinate cases, 11 patients are living and well for 5 or more years (60 per cent). In 8 of 13 patients the disease recurred after local excision or resection, resulting in amputation. Five of the 8 patients died of their disease, while 3 are living and well 5 years or more. Three primary amputees are 5 year survivals, without disease.

Bold, ablative surgery by resection or amputation is necessary to cure parosteal osteoma, in the majority of cases. If complete resection in a relatively inactive lesion can be accomplished, cure should result. There is no place for temporizing surgical excisions. If there is any question about adequate en bloc resection, then amputation is indicated. When pathologic changes show frank sarcoma, amputation is indicated at once. Recurrent cases, with or without malignant manifestations, are best treated by amputation.

Care should be exercised not to confuse parosteal osteoma with osteogenic sarcoma situated predominantly in the periosteal zone of long bone structure. The differential diagnosis also includes atypical myositis ossificans, certain osteochondromas, and osteomas.

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THE HUMORAL FACTOR IN REGENERATION OF THE LIVER IN PARABIOTIC RATS

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THE FACTORS influencing regenerative hyperplasia in the residual liver after subtotal hepatectomy could be several. There would be the local factor of wound repair which obtains in any tissue, visceral or somatic. The incitation to tissue growth consequent to tissue injury could be simply reparative or exuberant and regenerative as it seems to be commonly in the case of the liver. Nutritive factors and vascular intactness, even the increased extrahepatic portal venous pressure, influence the rapidity and completeness of liver regeneration as we have shown. Are there systemic factors such as the pituitary "drive" for example, influencing such regenerative hyperplasia? Clinical evidence in the human after total right hepatic lobectomy suggests, and experimental evidence in dogs following the same operation has demonstrated that the exhibition of cortisone postoperatively augments the growth of the residual liver. The true existence of a humoral factor might be effectively demonstrated in parabiotic rats, in only one of which a hepatectomy would be done.

Bucher, Scott, and Aub performed partial hepatectomies on 1 partner of each of 14 parabiotic pairs, using rats of Wistar stock. They also did it on 2 partners of each of 3 sets of parabiotic triplets at intervals of 48 and 72 hours later. The intact livers of the nonhepatectomized partners all exhibited a higher mitotic rate than the controlled livers removed at the time of hepatectomy. In parabiotic twins the main value was 6 times, and in triplets it was 50 times that of the controls. Two of the 14 pairs were sacrificed within 24 hours and in these animals no significant alteration occurred in the livers of the nonhepatectomized partners. The evidence suggested that in regenerating rat liver, mitosis is initiated or modified by alterations in the composition of the blood.

From Gastric Service, Memorial Center for Cancer, Sloan-Kettering Institute for Cancer Research, André and Bella Meyer Physiology Laboratory, New York, and Division of Laboratories and Research, New York State Dept. of Health, Albany.

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EXPERIMENTAL PROCEDURE

The following experiments were conducted to investigate the humoral factor in regeneration of the liver. Twelve parabiotic pairs of rats were prepared. The rats used in this experiment were male and female, but both partners of each pair were of the same sex. The hair was removed from the left half of the body of one and the right half of the other with an electric shaver. The area from which the hair was removed extended from a point 2 centimeters behind the ear to 3 centimeters from the base of the tail. These animals were then anesthetized with ether and the areas from which the hair had been removed were washed with alcohol. They were placed upon sterile cloths and under aseptic precautions a longitudinal incision was made on each animal from a point 4 centimeters from the base of the tail to a site near the ear. At this point the ventral edges of the two skin incisions were united by suturing. The abdominal wall was then incised from the region just ventral to the anterior end of the iliac bone to the margin of the ribs. Care was taken not to open the chest or cut into the diaphragm. The abdominal cavities of the two animals were then united peritoneum

TABLE I.—TABULATION OF QUANTITATIVE CHARACTERISTICS OF THE PARABIOTIC RATS, THEIR LIVERS, AND THE REGENERATING LIVERS FOLLOWING 70 PER CENT PARTIAL HEPATECTOMY IN ONE OF EACH TWINNED PAIR

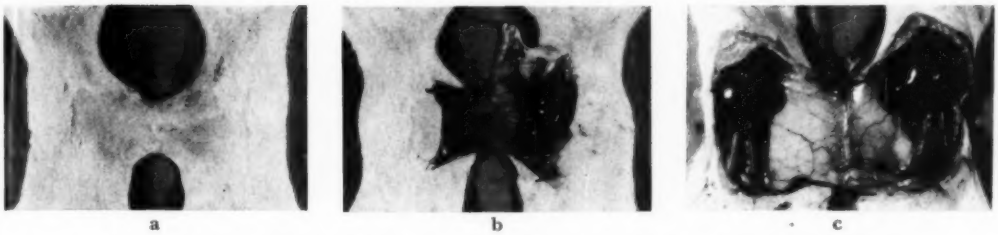
	A *Control tissue obtained by 70 per cent partial hepatectomy of one member of parabiotic twins*	*B* *Parabiotic twin 48 hrs. after 70 per cent partial hepatectomy*	*C* *Intact parabiotic twin 48 hrs. after 70 per cent partial hepatectomy in opposite twin*	*D* *Parabiotic twin 72 hrs. after 70 per cent partial hepatectomy*	*E* *Intact parabiotic twin 72 hrs. after 70 per cent partial hepatectomy in opposite twin*
1 No. of animals used	2	3	3	2	2
2 Average, in gms. of measured masses of animals	449 *438 459 479*	459 *431 450 475*	452 *415* 431*	423 *404 423*	414
3 Average of per cents of parenchymal cells in mitosis	0.0184 *0.0273 0.0095*	0.127 *0.1049 0.1280 0.1482*	0.0054 *0.0038 0.0041 0.0083*	0.2326 *0.1543 0.3107**	0.002 *0.000 0.004*
4 Average, in gms. of estimates of masses of initially intact livers	16.43 *15.70 16.44 17.16*	16.18 *15.42 16.12 17.00*	15.15 *14.86* 15.44*	14.81 *14.46 15.16*	
5 Average, in gms. of measured masses of livers intact at end of experiment	17.89 *16.98 17.38 19.32*	16.59 *15.97 17.21*			
6 Difference between row 5 and row 4	1.71 *1.26 1.56 2.32*	1.78 *1.51 2.05*			
7 Average, in gms. of measured masses of liver excised with 70 per cent partial hepatectomy	10.97 *10.60 10.97 11.35*	10.13 *9.90* 10.35*			
8 Average, in gms. of estimates of masses of initially residual livers after 70 per cent partial hepatectomy	5.46 *5.10 5.47 5.81*	4.83 *4.56* 5.09*			
9 Average, in gms. of measured masses of livers of animals with residual and regenerating liver	7.11 *6.85 7.10 7.38*	8.90 *8.30* 9.50*			
10 Average, in gms. of estimated increments of regenerated livers: difference between row 9 and row 8	1.65 *1.57 1.63 1.75*	4.07 *3.74* 4.41*			

Italicized figures are values for the individual animals.
*This liver showed histologic evidence of some focalized acute inflammatory reaction.

to peritoneum, muscle to muscle, fascia to fascia, and skin to skin using No. 1 silk. This reinforcement between the partners was performed by the method of Bunster and Meyer. The scapula of each animal was located and the skin and subcutaneous connective tissue were freed from the dorsal surface without cutting or displacing the muscles. The left shoulder blade of the right animal and the right shoulder blade of the left animal were raised and sutures were placed through the pectoral muscles and supraspinous fossae of the scapulas; the lateral aspects of the scapulas of the two animals were then firmly approximated by securely tying the two free ends of the sutures.

These parabiotic animals did not receive any special postoperative diet. Penicillin was given for 3 postoperative days. The only complications were wound infection in 1 animal and intestinal obstruction in 2 others, resulting from displacement of bowel into the body cavity of the other partner thus causing strangulation. Otherwise the remaining parabiotic twins lived and gained weight.

Three months after the operation the animals had completely convalesced, were adjusted to their unnatural union, and the collateral circulation was well established. When ether anesthesia was given to one partner, the other also became anesthetized.



a b c

FIG. 1. a, Parabiotic rats 3 months after celioanastomosis. b, Operative scene prior to 70 per cent partial hepatectomy in one member of a pair of parabiotic rats. c, Parabiotic twinned rats at sacrifice 72 hours posthepatectomy to show: (1) the residual and regenerating liver of the 70 per cent hepatectomized animal and (2) the intact liver of the opposite member.

Under anesthesia a right lateral abdominal incision was made in the right partner and a 70 per cent partial hepatectomy was performed by the technique previously mentioned. This extirpated normal liver tissue was conserved for use as a controlled histologic study. Forty-eight hours later in 4 pairs and 72 hours later in another 5 pairs these parabiotic animals were again anesthetized and transverse incisions were made over the communicated region of the abdominal walls. When the peritoneal cavity was opened the peritoneum, muscle, and skin had healed nicely. The remaining liver of the partially hepatectomized partner was somewhat larger than the residual organ left after the 70 per cent hepatectomy. The intact liver of the other partner was darker in color and more congested (Figs. 1a, b, and c).

Small pieces of the excised liver were fixed with 10 per cent formalin, embedded in paraffin, sectioned at 6 microns, and stained with Harris' hematoxylin and eosin. These preparations were examined at a magnification of 970 diameters with an oil immersion objective. Parenchymal cells having intact nuclei in the entire field at this magnification were counted. The average of 10 such fields was determined. The sections of liver on a particular slide were then systemically searched with the assistance of a mechanical stage. No field was used which contained any significant blood vessel or duct. Between 25,000 and 100,000 parenchymal cells were counted from each animal. For a cell to be counted the nucleus had to have an intact rim in the plane of section. A cell was counted, when in mitosis, if its nucleus had definite chromosomal figures in metaphase, anaphase, and telaphase, or if the nuclei were definitely in late prophase. Inasmuch as any resting incomplete nucleus was not counted in determining the average of a field, no mitotic figure was counted if the chromosomes were fragmentary and few, an occurrence resulting from the plane of section leaving only a small portion of the nucleus on the slide.

RESULTS OF THE EXPERIMENT

The results of the counts are tabulated together with other pertinent data in Table I and in Figures 2 and 3. Referring to Figure 2, it is observed that the rate of mitosis in the livers of the intact parabiotic partners is at the most equal or even slightly less than the rates in the livers of normal individual controls. These data do not support the conclusion of Bucher, Scott, and Aub that, "the intact livers of the nonhepatectomized partners *all* exhibited a higher mitosis rate than the control livers removed at the time of hepatectomy." Their conclusion was based on experiments conducted on 2 groups of animals, one prepared according to the Bunster-Meyer technique and the other group with celioanastomosis and splenic juncture. An explanation of the contradiction in their results and those of the present investigators may be found in the possibility that the celioanastomosis and

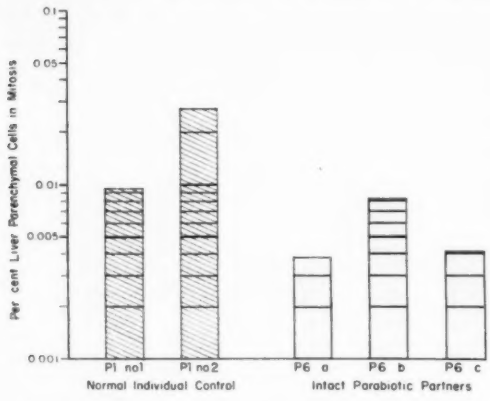


FIG. 2. A logarithmic comparison of per cents of parenchymal cells in mitosis from normal rat liver obtained at the time of partial hepatectomy of one of the parabiotic rats with liver from an intact parabiotic twin whose opposite partner 48 hours earlier had undergone 70 per cent partial hepatectomy. Data from Table I, line 3, columns A and C.

splenic juncture may permit the passage of portal blood from one rat to the other rat. Bucher said the passage of blood vessels through this splenic juncture could not be positively demonstrated under the microscope. The possibility of this occurrence, however, suggests that augmented portal blood flow in the nonhepatectomized partner could be the factor which caused the great increase in the mitotic rate in the intact partner of Bucher, Scott, and Aub's pair No. 25. We have previously shown that experimental hepatic regeneration is intimately linked with the quantity of portal blood traversing the organ. Our earlier experiments indicated that the rapidity of regenerative hyperplasia of the residual liver tissue, other conditions being on a par, is directly proportionate to the degree of portal hypertension.

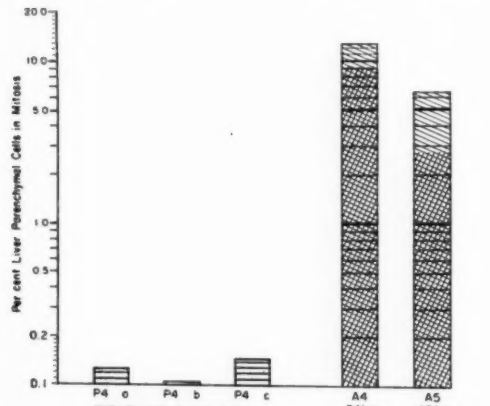
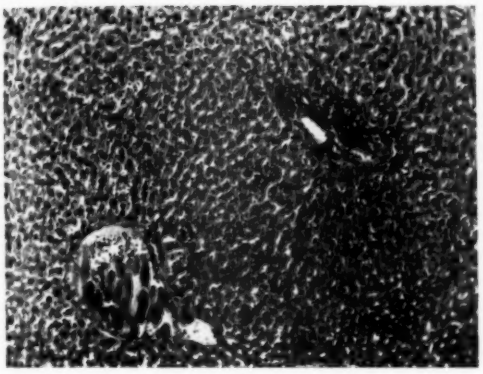


FIG. 3. A logarithmic comparison of per cents of parenchymal hepatic cells in mitosis taken 48 hours after 70 per cent partial hepatectomy of parabiotic rats (with intact partners), with the livers of 70 per cent partially hepatectomized individual rats.

Three pairs of parabiotic triplets were used by Bucher, Scott, and Aub in which 75 to 80 per cent of the livers of 2 members were excised with the central animal intact. A celioanastomotic technique was used, but no comment is made about splenic anastomosis. In their table and chart the mean average of the hepatic cells in mitosis in the nonhepatectomized partner is on the average 50 times greater than that in the control.

Bucher's conclusion that, "the evidence suggests that in regenerating rat liver, mitosis is initiated by alterations in the chemical composition of the blood," cannot be disproved. Certain other areas of evidence not previously discussed may be presented. From the data in the present experiment, the mitotic rate in the 70 per cent partially hepatectomized parabiotic partners was only from 1/20 to 1/100 that of individual partially hepatectomized rats. (Bucher and associates stated that they did not count mitotic figures in the regenerating livers of the partially hepatectomized partners but they thought "they were present in sufficient numbers to indicate that active proliferation was in progress." Their measurement of liver mass, however, showed regeneration apparently to proceed at the same rate as that of normal separated rats.)

A second area is comparison of the percentage of liver regeneration in the individual partially hepatectomized animal with the regeneration in the partially hepatectomized parabiotic having an intact partner.



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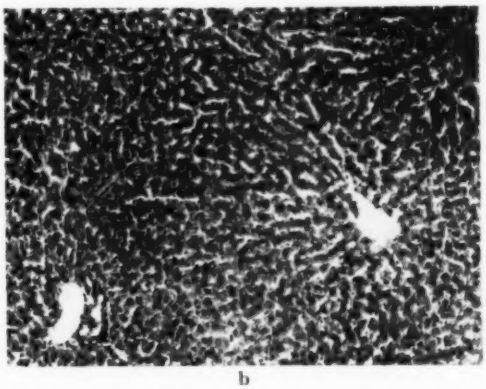

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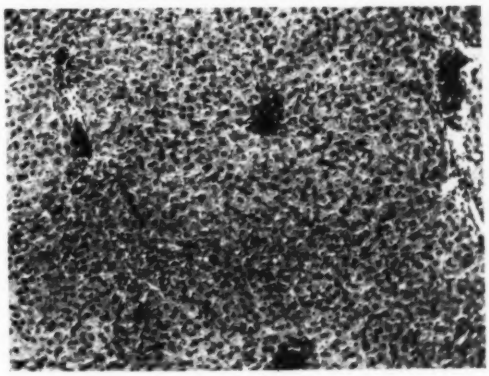

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FIG. 4. a, Control. Rat liver excised at the time of 70 per cent partial hepatectomy from one parabiotic twin. Normal hepatic parenchyma surrounds a central vein in the lower left quadrant and a portal tributary in the upper right quadrant. b, Specimen of liver removed from the 70 per cent partially hepatectomized parabiotic partner, 48 hours after the operation. The sinusoids are more distended than in the control liver. Hematoxylin and eosin, × 22. c, Rat liver from the intact parabiotic twin, obtained 48 hours after the 70 per cent partial hepatectomy in the opposite partner. Portal areas are seen laterally and central veins are viewed in the middle. The parenchyma appears normal. The sinusoids are not distended as in the liver of the partially hepatectomized partner. Hematoxylin and eosin, × 22.

Using the data in Table I, row 7 with that in row 8, and columns B and D of Table I, an estimate can be approximated of the original liver mass. This estimate, with the data in row 9, permits one to calculate the estimated regenerated liver in the parabiotic twins 48 hours and 72 hours after 70 per cent partial hepatectomy. The value for 48 hours with our data is 43.3 per cent and for 72 hours it is 59.4 per cent. Individually, 70 per cent partially hepatectomized rats in our laboratory, under the same conditions, had a restoration of 57.8 and 69 per cent for two values for animals 48 hours postpartial hepatectomy. For animals 72 hours postpartial hepatectomy, there is 1 value of 76 per cent and 1 value of 65.6 per cent. This observation suggests that our rats which were partially hepatectomized when parabiotic had a slower rate of liver mass regeneration than did our individual partially hepatectomized rats. This finding corresponds with the low mitotic rates observed in our parabiotic animals.

SUMMARY

In these experiments it was observed that the intact parabiotics' partially hepatectomized partner exhibited a slower rate of hepatic regeneration than the individually partially hepatectomized rat as determined by an estimated amount of liver regeneration and as determined by an actual mitotic rate count. These observations differ from the results given by Bucher, Scott, and Aub for estimated weights of liver regeneration and for their impressions of mitotic activity in the regenerating liver of the parabiotic partially hepatectomized rats.

The data in the experiments reported

herein do not contradict the idea that there is a humoral factor influencing the rate of liver regeneration, but instead offer additional evidence for the support of this thesis. In previous experiments we have demonstrated that the larger the proportion of the liver excised, the greater is the rapidity and the more complete the regeneration experienced. Within the limits of survival, it is proper to make the general statement that the stimulus to hepatic regeneration is directly proportionate to the percentage of liver excised. For example, in the experimental ablation of 55 per cent and 70 per cent of the liver in two series of rats, we have found that in the group with the smaller residual livers (i.e., after 70 per cent resection) the livers regenerate more quickly, and at the end the rats in this group have larger and heavier livers than are found in the group experiencing more conservative (i.e., 55 per cent) hepatectomies. The parabiotic rats, with commingling circulation of blood, therefore, have adequate liver tissue between them, so that even after major hepatectomy in one partner the impulse to liver regeneration is less than in the individual rat having liver resection of comparable degree.

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WOUND HEALING

II. An Evaluation of Surgical Suture Material

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THE IDEAL SURGICAL SUTURE would consist of material which would permit use in any operation, the only variable being the size as determined by the required tensile strength. It should handle comfortably and naturally to the surgeon. The tissue reaction stimulated should be minimal and, above all, should not create a situation favorable to bacterial growth. Tensile strength should be high in small caliber. A knot should hold without fraying or cutting. The material should be easy to thread and not shrink or fray. It should be nonelectrolyte, noncapillary, nonallergenic, and noncarcinogenic. The suture should be inexpensive. Sterilization should be accomplished easily by boiling or autoclaving without alteration of the suture. The material might also be absorbed with minimal tissue reaction after it has served its purpose. Obviously, this ideal surgical suture material is not available.

Many studies of sutures have been published; one of the most comprehensive was that of Localio, Casale, and Hinton. These authors compared catgut sutured wounds with wounds closed with silk, cotton, wire, or nylon. With catgut, the lag period was prolonged and final healing delayed in the abdominal wounds of rats because of the more marked inflammatory reaction which occurred. A more recent outstanding study was that of Madsen. He first investigated the reaction of the tissues to various sutures, then later the amount of retained tensile strength in loops of suture in fascia, and finally reported a clinical analysis of wound complications in 1,211 patients after closure with plain catgut, chromic catgut, or perlon. Madsen found that plain catgut produced a marked exudative tissue reaction with a wide reaction zone and a delayed formation of collagen. This reaction to plain catgut decreased the tensile strength of the wound, the tensile strength of the suture diminished rapidly because of suture absorption, and the knots tended to slip. The fine nonabsorbable suture materials stimulated slight exudation, a small reaction zone, and a rapid formation of collagen. Accordingly, the strength of the tissue was not much impaired, the suture retained its tensile strength, and the knots were safe (except with monofilament synthetic fibers). The tanned absorbable sutures behaved almost like the nonabsorbable material during the first days after insertion. Subsequent to disappearance of the tanning chemical, however, a retarded absorption with marked exudation took place. With this ex-

TABLE I.—AVERAGE DIAMETER OF SUTURES

Suture	*Diameter, mm.*
No. 4-0 silk	0.3027
No. 4-0 cotton	0.2466
No. 4-0 dacron	0.2386
teflon	0.2147
No. 4-0 nylon	0.2149
nymo	0.1762
ramie	0.2400
No. 32 wire	0.1976
No. 4-0 chromic	0.2302
No. 2-0 silk	0.3587
No. 2-0 plain	0.3952
No. 2-0 chromic	0.3953
No. 1 silk	0.5541

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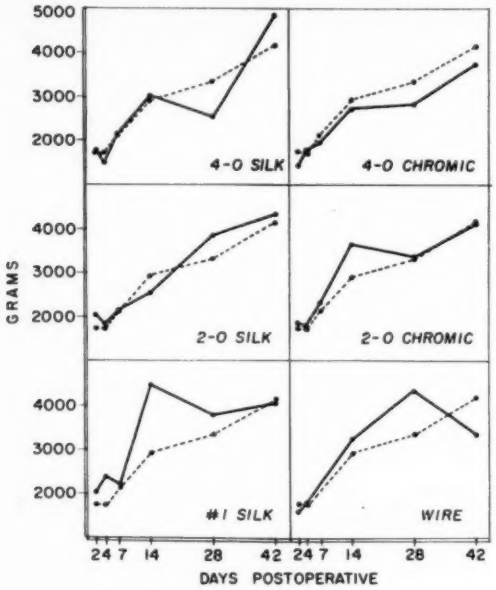

FIG. 1.

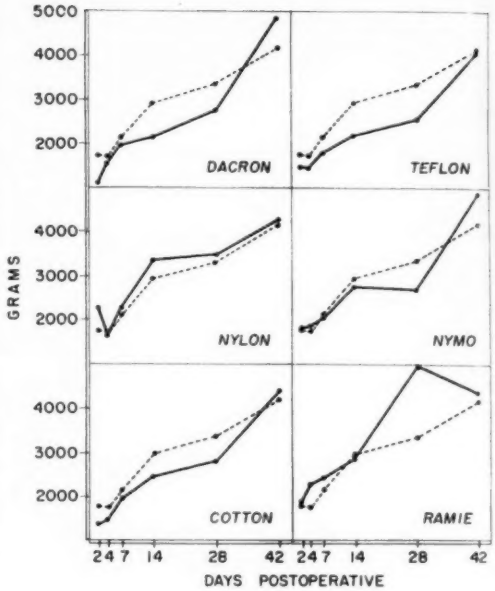

FIG. 2.

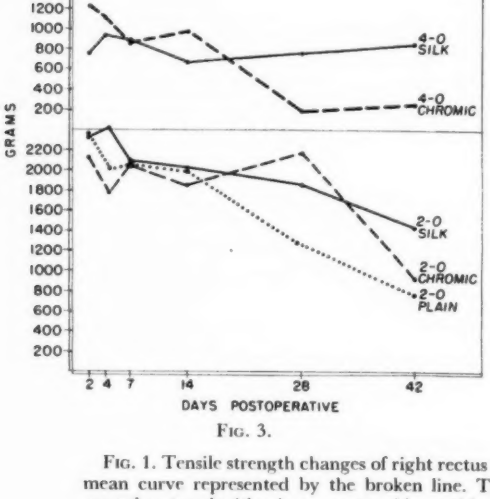

FIG. 3.

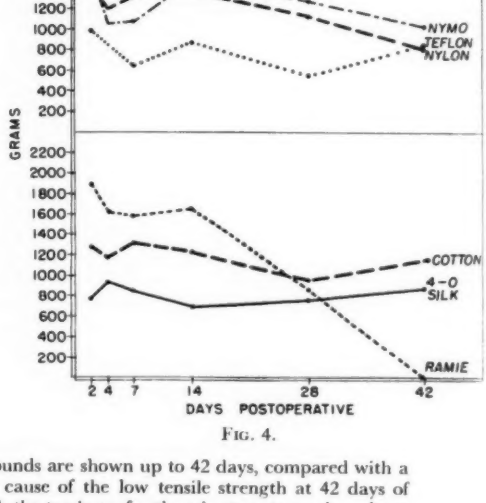

FIG. 4.

FIG. 1. Tensile strength changes of right rectus wounds are shown up to 42 days, compared with a mean curve represented by the broken line. The cause of the low tensile strength at 42 days of wounds sutured with wire was not evident, although the tendency for the wire to cut may have been a factor (see Fig. 12).

FIG. 2. Tensile strength changes of right rectus wounds are shown up to 42 days compared with a mean curve represented by the broken line.

FIG. 3. Comparative tensile strength of absorbable and nonabsorbable sutures. Changes in tensile strength of the implanted loops of suture are shown. The tensile strength of the catgut sutures decreased considerably after 14 days.

FIG. 4. Comparative tensile strength of nonabsorbable sutures. The tensile strength of the implanted suture loop showed no decrease for silk, cotton, dacron, and teflon.

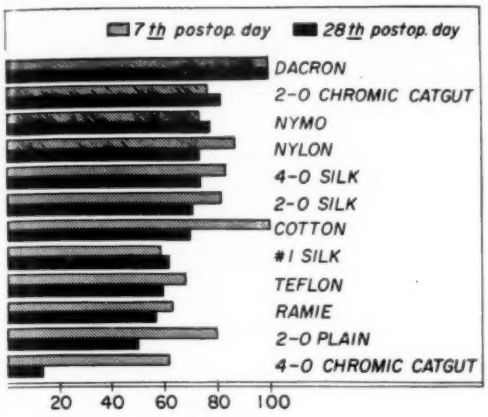

FIG. 5.

FIG. 5. The percentage of the original tensile strength retained on the seventh and twenty-eighth postoperative days is shown, arranged in decreasing per cent retained on the twenty-eighth day.

FIG. 6. Comparison of tissue reaction of nonabsorbable sutures. Grading of tissue reaction to implanted loop of suture after the initial inflammatory reaction subsided, the nonabsorbable sutures uniformly produced very little tissue reaction. Teflon caused the lowest grade reaction.

FIG. 7. Comparison of tissue reaction of absorbable and nonabsorbable sutures. Grading of tissue reaction to implanted loop of suture, the pattern of the grade of tissue reaction to catgut sutures was altered by the inflammatory reaction as absorption of the suture occurs.

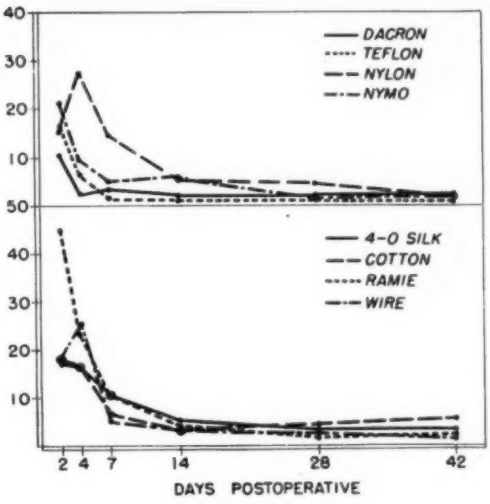

FIG. 6.

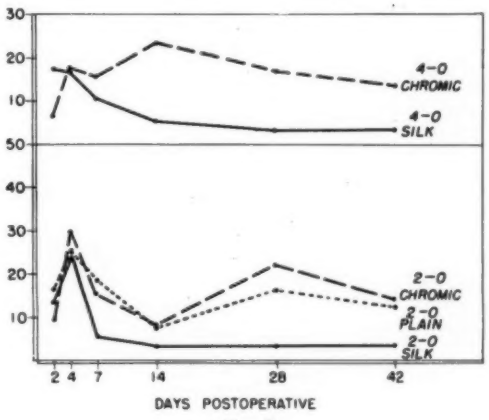

FIG. 7.

perimental background, the clinical study of 1,211 patients was done, with the finding that all types of wound complications except suture extrusion were fewer with nonabsorbable suture materials. Madsen concluded that the nonabsorbable sutures were generally preferable and noted that some of the new synthetic fibers showed promise.

Recently, considerable interest in the tissue reaction to synthetic fiber materials has been evident from the standpoint of their use as blood vessel replacements, but only a few studies have been concerned with surgical sutures. Harrison, Swanson, and Lincoln (4) implanted squares of woven nylon, dacron, orlon, ivalon, and teflon in dogs and studied the reaction at intervals up to a year. Teflon was found to produce the least tissue reaction, both acute and chronic. Harrison in a later article (3) described the results of long term aorta grafts of various materials in dogs. Nylon grafts lost 85 per cent of the initial tensile strength in 175 days; dacron after 180 to 445 days lost 2.4 to 3.0 per cent; orlon in 180 days decreased 6.9 per cent; teflon decreased 1.7 per cent in 358 days. Teflon, the most inert synthetic material known, incited minimal tissue reaction. Usher and Wallace recently reported the effects of placing pellets or shredded yarn in the peritoneal cavity of dogs. Nylon, orlon, dacron, teflon, and marlex were studied. The two latter materials showed considerably less foreign body

TABLE II.—RESULTS WITH NO. 2-0 CHROMIC

Days postop.	No. anim.	Wound tensile strength: No. tests	Range	Mean	Suture tensile strength: No. tests	Range	Mean	Grade of tissue reaction: No. graded	Range	Mean
2	5	15	1183–2712	1887	5	1614–2679	2126	10	9–14	9.5
4	3	9	1000–2229	1714	6	1317–2339	1777	4	26–37	30.0
7	3	8	1691–3775	2310	6	1635–2436	2049	14	4–38	15.4
14	4	8	2999–4162	3659	4	1027–2289	1843	8	2–17	8.1
28	7	20	2096–4894	3385	14	1062–2798	2190	22	5–47	22.3
42	3	9	2099–7799	4111	11	656–1136	920	12	10–23	14.2

TABLE III.—RESULTS WITH NO. 2-0 PLAIN

Days postop.	No. anim.	Wound tensile strength: No. tests	Range	Mean	Suture tensile strength: No. tests	Range	Mean	Grade of tissue reaction: No. graded	Range	Mean
2	3	9	1298–2392	1894	6	2033–2765	2369	10	9–30	16.3
4	3	9	720–1751	1359	4	1369–2252	2002	9	21–37	25.3
7	3	9	1696–2257	2005	6	1310–2518	2050	10	3–39	18.6
14	4	12	2280–4694	3285	8	1045–2677	1988	12	2–27	7.8
28	6	18	1952–4902	3162	11	434–2200	1273	14	3–42	16.4
42	4	12	2289–6485	4007	16	480–1324	786	18	3–36	12.2

TABLE IV.—RESULTS WITH NO. 4-0 CHROMIC

Days postop.	No. anim.	Wound tensile strength: No. tests	Range	Mean	Suture tensile strength: No. tests	Range	Mean	Grade of tissue reaction: No. graded	Range	Mean
2	3	9	814–2423	1401	6	902–1384	1207	12	1–17	6.8
4	3	9	1114–2493	1760	6	961–1357	1120	11	2–43	17.0
7	3	9	1376–2699	1997	6	280– 999	847	5	4–27	15.6
14	3	9	2040–3197	2728	6	577–1240	897	9	11–37	23.2
28	6	18	2066–3512	2809	9	280– 624	196	26	4–64	17.0
42	4	12	2775–5528	3729	9	60– 612	272	15	4–45	13.1

TABLE V.—RESULTS WITH NO. 4-0 SILK

Days postop.	No. anim.	Wound tensile strength: No. tests	Range	Mean	Suture tensile strength: No. tests	Range	Mean	Grade of tissue reaction: No. graded	Range	Mean
2	5	10	1181–2906	1766	5	718– 884	774	9	6–23	17.2
4	5	24	952–2231	1498	21	827–1056	935	17	4–31	16.7
7	5	10	1760–2797	2107	5	793– 921	873	9	5–24	10.1
14	5	10	1971–3951	3007	5	622– 743	674	8	2–19	5.6
28	5	15	1515–3048	2551	10	479– 952	771	16	2– 6	3.2
42	3	9	3966–5130	4827	6	586– 988	863	14	2– 8	3.5

TABLE VI.—RESULTS WITH NO. 2-0 SILK

Days postop.	No. anim.	Wound tensile strength: No. tests	Range	Mean	Suture tensile strength: No. tests	Range	Mean	Grade of tissue reaction: No. graded	Range	Mean
2	4	12	1026–2985	2027	8	2142–2457	2318	14	6–41	13.9
4	5	15	1188–2725	1814	10	2150–2980	2419	19	11–44	23.7
7	6	18	1471–2924	2117	12	955–2396	2090	18	3– 7	5.7
14	5	12	1624–3220	2508	4	1801–2196	2020	21	2– 7	3.5
28	4	12	2315–5347	3898	8	1164–2208	1847	11	2– 5	3.3
42	4	12	2647–4516	3515	10	1000–1716	1424	20	2– 6	3.4

TABLE VII.—RESULTS WITH NO. 1 SILK

Days postop.	No. anim.	Wound tensile strength: No. tests	Range	Mean	Suture tensile strength: No. tests	Range	Mean	Grade of tissue reaction: No. graded	Range	Mean
2	3	9	1420–2879	2006	12	1817–3113	2636	21	17–65	39.7
4	3	9	1371–2887	2400	12	1911–2803	2317	11	24–58	39.4
7	3	9	1471–2998	2133	12	2211–2933	2521	20	22–77	45.7
14	3	10	2289–6723	4453	12	2272–2883	2425	18	4– 5	4.8
28	4	12	2649–6129	3769	14	2015–3959	2652	27	5– 9	6.3
42	4	13	2712–5676	4037	16	1792–2860	2355	28	4– 7	5.4

TABLE VIII.—RESULTS WITH COTTON

Days postop.	No. anim.	Wound tensile strength: No. tests	Wound tensile strength: Range	Wound tensile strength: Mean	Suture tensile strength: No. tests	Suture tensile strength: Range	Suture tensile strength: Mean	Grade of tissue reaction: No. graded	Grade of tissue reaction: Range	Grade of tissue reaction: Mean
2	3	9	1054–2210	1351	6	1206–1346	1263	10	17–22	17.9
4	3	9	666–2048	1459	6	1020–1353	1189	10	9–22	16.8
7	3	8	1573–2687	1925	4	1316–1388	1330	7	3–20	6.6
14	4	12	1645–3067	2425	8	1003–1435	1222	9	2– 5	3.1
28	4	12	1997–3271	2786	8	675–1391	958	12	4– 6	4.3
42	4	12	3040–6229	4384	16	681–1445	1173	20	4–14	5.4

TABLE IX.—RESULTS WITH RAMIE

Days postop.	No. anim.	Wound tensile strength: No. tests	Wound tensile strength: Range	Wound tensile strength: Mean	Suture tensile strength: No. tests	Suture tensile strength: Range	Suture tensile strength: Mean	Grade of tissue reaction: No. graded	Grade of tissue reaction: Range	Grade of tissue reaction: Mean
2	3	9	1569–2317	1883	7	1594–2166	1890	14	38–57	45.0
4	3	9	1533–2720	2238	12	1200–1890	1614	16	11–31	23.3
7	3	9	1433–3066	2402	12	1242–2077	1595	19	5–17	10.3
14	3	9	1494–5140	2842	4	1201–2300	1654	17	3– 7	4.7
28	4	12	3608–6375	5026	10	976–2300	1431	21	1– 4	1.8
42	4	12	2667–6885	4314	8	0– 0	0	29	1– 6	2.6

TABLE X.—RESULTS WITH NYLON

Days postop.	No. anim.	Wound tensile strength: No. tests	Wound tensile strength: Range	Wound tensile strength: Mean	Suture tensile strength: No. tests	Suture tensile strength: Range	Suture tensile strength: Mean	Grade of tissue reaction: No. graded	Grade of tissue reaction: Range	Grade of tissue reaction: Mean
2	3	9	1893–3249	2255	12	1208–1543	1422	18	6–24	15.4
4	3	9	880–2881	1671	11	880–1669	1194	10	18–39	27.8
7	3	9	293–3052	2268	11	1017–1528	1326	19	10–24	14.4
14	3	9	2295–4200	3393	11	1176–1590	1384	19	2– 9	5.1
28	4	12	2443–5759	3452	15	962–1377	1128	32	3– 6	4.5
42	4	12	1696–5624	4244	14	224–1232	815	22	1– 6	1.3

TABLE XI.—RESULTS WITH NYMO

Days postop.	No. anim.	Wound tensile strength: No. tests	Wound tensile strength: Range	Wound tensile strength: Mean	Suture tensile strength: No. tests	Suture tensile strength: Range	Suture tensile strength: Mean	Grade of tissue reaction: No. graded	Grade of tissue reaction: Range	Grade of tissue reaction: Mean
2	3	9	1209–2562	1777	12	1356–1784	1576	10	14–37	21.4
4	3	9	829–2577	1847	12	797–1558	1157	19	5–29	9.6
7	2	6	1400–2655	2033	7	934–1465	1182	11	2–11	5.0
14	3	8	1880–4386	2743	8	1106–1634	1469	16	1–29	5.7
28	3	9	2264–3018	2700	8	1112–1522	1274	16	1– 3	1.3
42	4	12	3012–9766	4874	13	764–1450	1029	23	1– 4	1.6

TABLE XII.—RESULTS WITH DACRON

Days postop.	No. anim.	Wound tensile strength: No. tests	Wound tensile strength: Range	Wound tensile strength: Mean	Suture tensile strength: No. tests	Suture tensile strength: Range	Suture tensile strength: Mean	Grade of tissue reaction: No. graded	Grade of tissue reaction: Range	Grade of tissue reaction: Mean
2	3	9	720–2213	1136	6	1321–1744	1523	5	9–18	10.8
4	3	9	1287–1911	1549	6	1286–1756	1609	4	2– 3	2.7
7	3	8	1536–2261	1946	5	1640–1744	1666	7	3– 4	3.1
14	3	8	1273–2924	2108	6	1449–1640	1516	8	2	2.0
28	3	8	2236–3274	2735	6	1548–1794	1692	10	2	2.0
42	4	12	3556–6106	4849	16	1579–1896	1724	22	2– 4	2.3

TABLE XIII.—RESULTS WITH TEFLON

Days postop.	No. anim.	Wound tensile strength: No. tests	Wound tensile strength: Range	Wound tensile strength: Mean	Suture tensile strength: No. tests	Suture tensile strength: Range	Suture tensile strength: Mean	Grade of tissue reaction: No. graded	Grade of tissue reaction: Range	Grade of tissue reaction: Mean
2	3	9	1159–2442	1472	12	914–1068	980	19	6–27	16.5
4	3	9	1160–2105	1447	12	620– 944	855	20	1–14	6.2
7	3	8	916–2375	1795	12	293– 895	635	21	1– 5	1.9
14	4	12	1456–3051	2174	12	670–1106	876	24	1– 2	1.1
28	4	12	2600–3748	3010	12	291– 831	565	24	1– 3	1.1
42	6	18	1828–5441	4098	16	693–1076	837	25	1	1.0

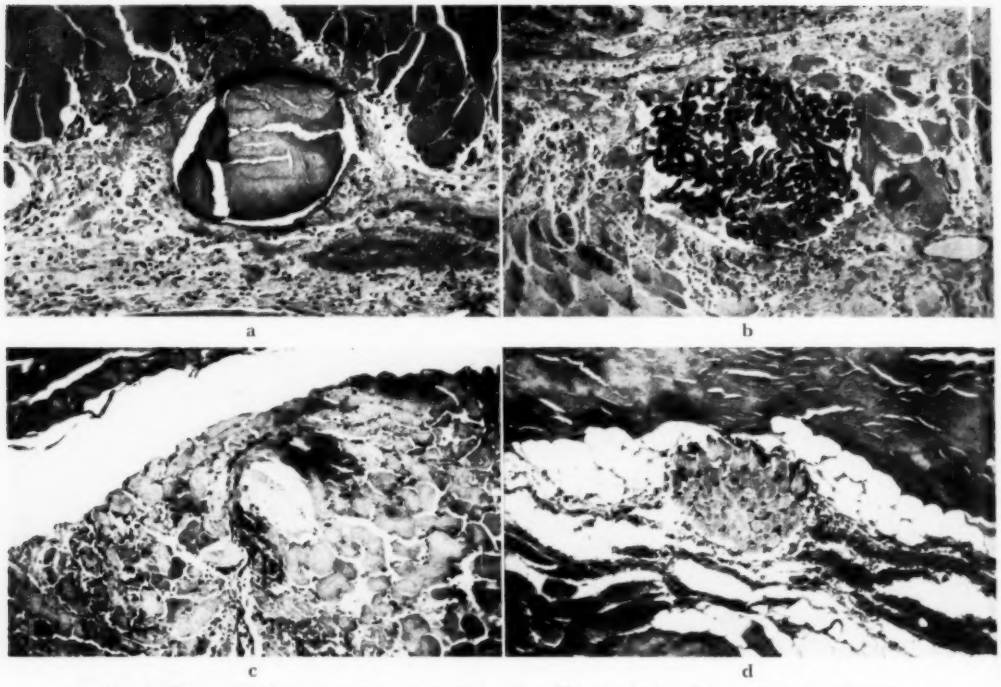

FIG. 8. Tissue reaction on second postoperative day. The similarity of the reaction to all sutures is evident. a, No. 4-0 chromic catgut. b, No. 4-0 silk. c, Wire. d, Teflon.

reaction than the others. Narat, Cangelosi, and Belmonte compared silk, cotton, and dacron in animals and used dacron in 89 operations. They found the tensile strength and frictional coefficient of dacron to be superior to that of cotton and silk. Dacron did not fray, was not affected by repeated autoclaving, and was well tolerated by the tissues. They concluded that dacron deserves an important place among nonabsorbable suture materials. Dettinger and Bowers implanted cotton, silk, nylon, dacron, and orlon subcutaneously in rats. Sections were made from 24 hours to 3 months after implantation, and a comparison was made based on the polymorphonuclear leucocyte response, cellular density, and width of tissue reaction. By these criteria, the synthetic fibers were less irritating to tissues, and dacron produced the least reaction.

The studies reported herein were carried out in order to compare surgical suture material by four criteria: tensile strength of the wound, histologic study of the wound, change in tensile strength of the suture, and histologic grading of the tissue reaction to the suture.

TABLE XIV.—RESULTS WITH WIRE

		Wound tensile strength			*Suture tensile strength*			*Grade of tissue reaction*		
Days postop.	*No. anim.*	*No. tests*	*Range*	*Mean*	*No. tests*	*Range*	*Mean*	*No. graded*	*Range*	*Mean*
2	3	9	924–1960	1598				7	9–24	17.1
4	3	9	1041–2120	1765				9	20–31	25.3
7	3	9	1755–2714	2431				13	3– 6	5.1
14	4	12	1637–5889	3225				14	1– 5	3.1
28	4	12	2850–5443	4318				15	1– 6	2.4
42	3	9	2289–4140	3361				11	1– 4	1.9

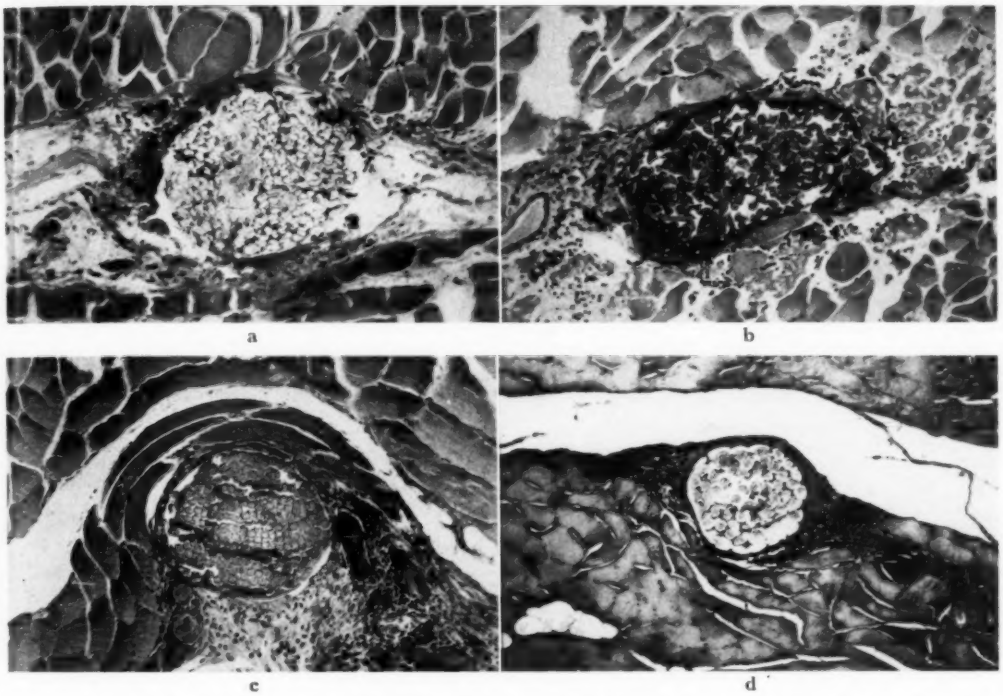

FIG. 9. Tissue reaction on fourth postoperative day. The reaction now consists mainly of large mononuclear cells and fibroblasts, with few remaining acute inflammatory cells. Cotton in "a" and silk in "b" show less extensive reaction than dacron in "c" and teflon in "d."

METHODS

The following sutures were studied: No. 4-0 chromic catgut, No. 2-0 chromic catgut, No. 2-0 plain catgut, No. 4-0 silk, No. 2-0 silk, No. 1 silk, No. 4-0 cotton, dacron, teflon, nylon, nymo, ramie, and No. 32 stainless steel wire. The average diameter is shown in Table I. Teflon was received from the manufacturer as a multifilament thread and, other than twisting to allow handling and sterilization, was used untreated. Nymo is made with 210 denier multifilament nylon containing 34 separate continuous filaments. These are bonded with a solution of nylon at an elevated temperature so as to "weld" the filaments together and impart a smooth coating. Ramie, as described by Coss and Taylor, is a plant fiber which after processing produces a fiber considerably longer than cotton, having greater tensile strength both wet and dry, greater resistance to flexing and shrinkage, and superior knotting strength.

New Zealand rabbits of 6 to 7 months of age were used. All operations were done with the usual aseptic technique. A long midline abdominal skin incision was made, skin flaps were raised, and then a long incision was made through the right rectus muscle into the peritoneum. The left side of the anterior abdominal wall was elevated, and several long loops of the suture under study were placed longitudinally in the left anterior abdominal wall musculature. The ends were tied very loosely to avoid any tension. The rectus incision was then closed with the same material. Interrupted sutures were placed through the anterior sheath, rectus muscle, and peritoneum at intervals of .7 to 1.0 centimeter with 0.3 to 0.5 cen-

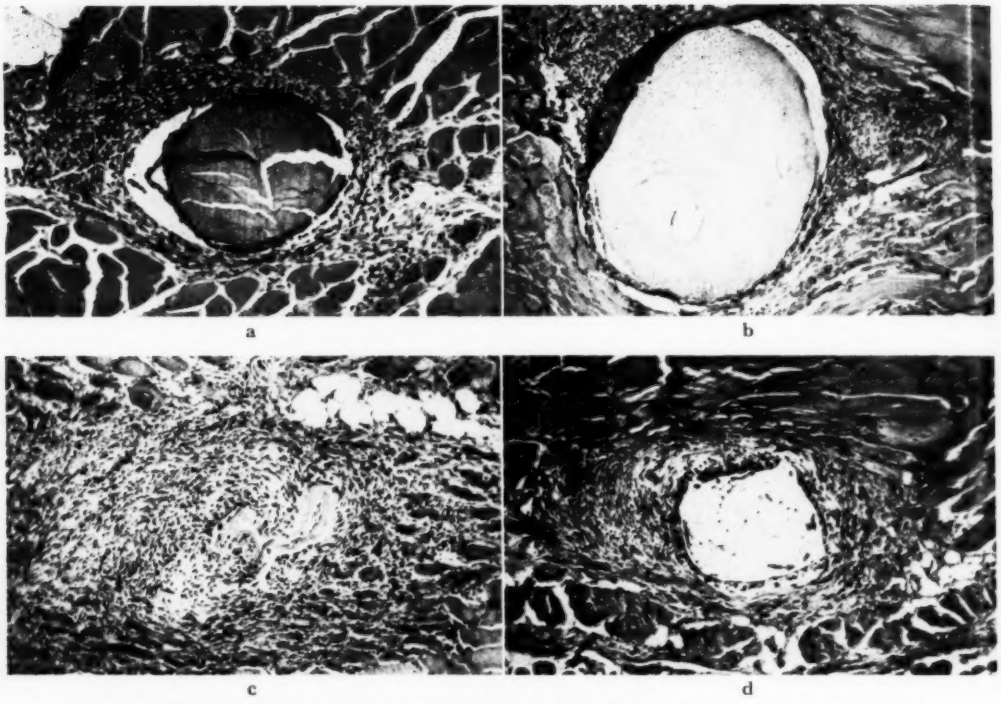

FIG. 10. Tissue reaction on seventh preoperative day. Absorption has not started in the No. 4-0 chromic catgut in "a" nor in the No. 2-0 plain catgut in "b," and mature fibrous tissue is being formed similar to that around wire in "c" and nylon in "d."

timeter of tissue on each side of the incision being included. Knots were tied only tightly enough to appose the edges. The superficial fascia and skin were closed with fine silk. No antibiotics were given and any gross infection resulted in discard of the animal.

At intervals of 2, 4, 7, 14, 28, and 42 days, the animals were anesthetized and the rectus wound was exposed. Strips 2 centimeters wide were cut transversely, and the tensile strength was immediately determined in a simple suspension system in which water was added to a container attached to the lower edge of the strip. A section of the left side of the abdominal wall was excised across one end of the suture loops and this, with a portion of the wound, was fixed for later staining with hematoxylin and eosin. The remaining suture loops (with the exception of wire) were carefully removed, and the tensile strength was determined. A system of grading of the wounds was established, based on the inflammatory reaction, fibroblastic proliferation, and collagen formation. Tissue reaction to the sutures was graded by the method of Sewell, Wiland, and Craver.

A total of 287 animals was studied, which provided 842 wound tensile strength determinations, 745 suture tensile strength determinations, and 272 wounds and 1,170 sutures for histologic grading.

RESULTS

The details of the results obtained are shown in Tables II to XIV. Figures 1 and 2 show graphically the tensile strength determinations of the wounds. A mean curve, represented by the broken line, was ob-

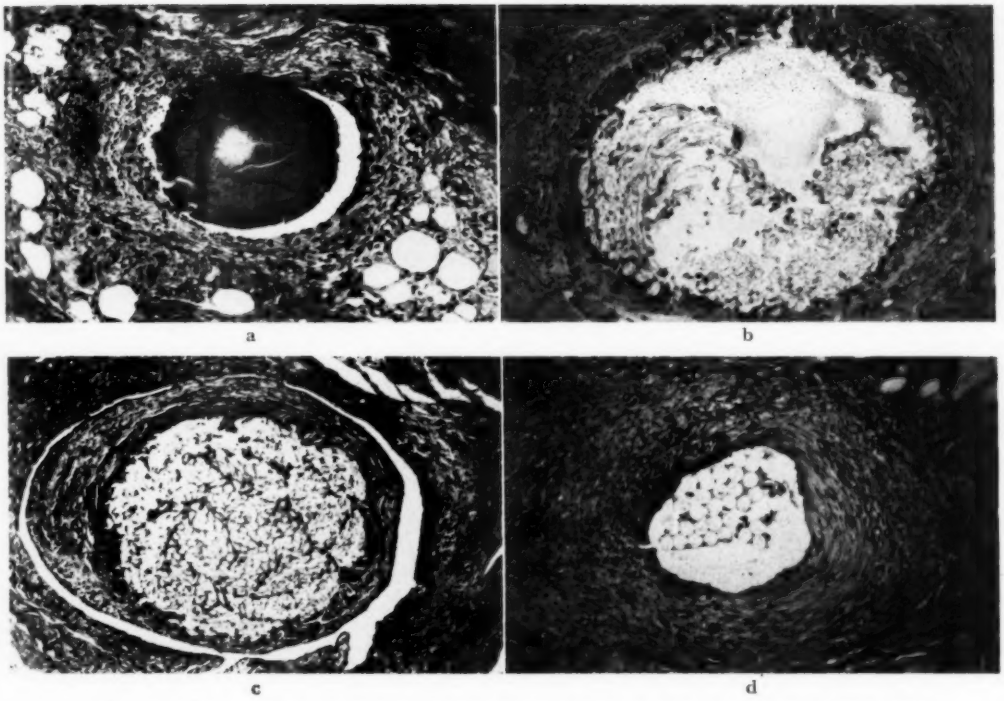

FIG. 11. Tissue reaction on fourteenth postoperative day. One edge of the No. 4-0 chromic catgut in "a" shows an irregularity representing the beginning of absorption. The cotton in "b" shows fluid about one side of the suture, and at points about the edge of the reaction individual fibers are being separated off from the main mass of suture by fibrous tissue. No. 2-0 silk in "c" shows a type of response noted occasionally, most often with silk, in which the suture is ensheathed in fibrous tissue within a second zone of scar tissue. The nymo in "d" shows almost entirely mature fibrous tissue.

tained by combining all of the wound tensile strength determinations plus others obtained in precisely similar studies, totalling 1,156 such tests. A lag period, in the concept of decreased tensile strength from the second to fourth postoperative day, was present with Nos. 4-0 silk, 2-0 silk, 2-0 chromic catgut, teflon, and nylon. No lag period was found with No. 4-0 chromic catgut, wire, cotton, and dacron; in each instance, the second day determination was below the mean. Nymo and ramie showed no lag period with the second day tensile strength being above the mean. The wound tensile strength determinations for No. 2-0 plain catgut are not shown as a graph but this followed closely the mean curve.

The system of grading utilized for study of the wounds resulted in no major differences. These studies with others in grading of wounds will be reported in a later communication.

A comparison of the tensile strength changes of the implanted suture loops is shown in Figures 3 and 4. The catgut sutures maintained their tensile strength well through the fourteenth day but by the forty-second day had lost considerable strength. Silk, cotton, dacron, and teflon lost very little strength during the period of observation. Nymo and nylon showed very similar curves of decrease. Ramie lost strength rapidly after the fourteenth day. The t-test for statistical significance of difference

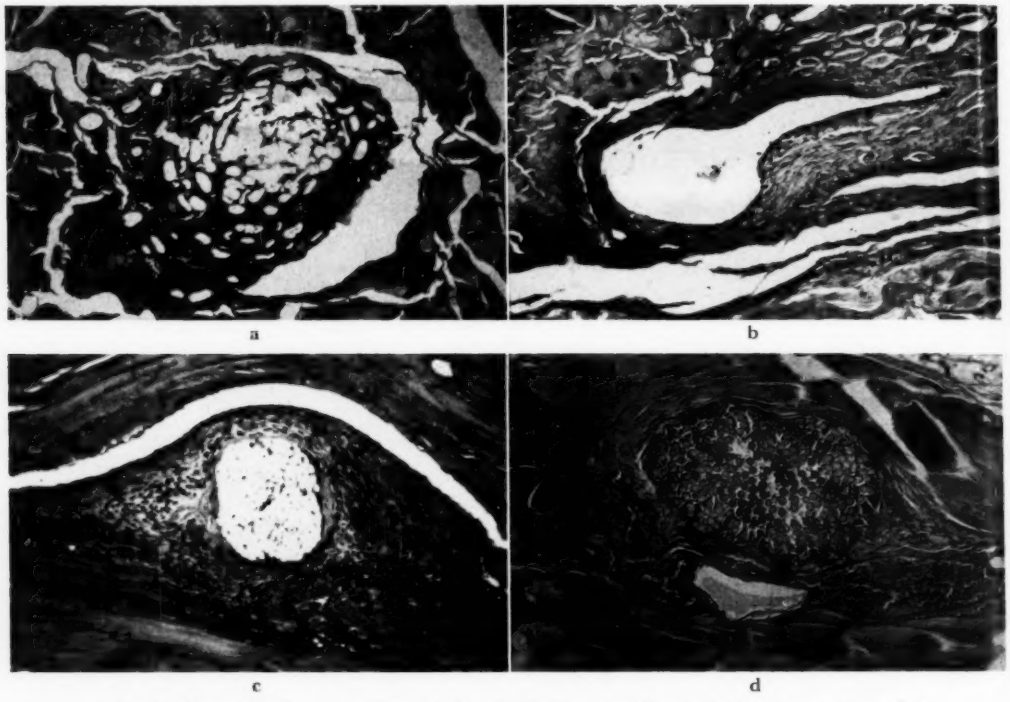

FIG. 12. Tissue reaction on twenty-eighth postoperative day. Ramie in "a" shows a type of fibrous tissue response also noted with cotton in which the fibers are separately surrounded. Wire in "b" shows the elongated slit at one end suggesting a tendency to cut. Dacron in "c" and teflon in "d" are encapsulated in scar tissue.

showed the No. 2-0 silk and the No. 2-0 chromic catgut to differ at 4 and 42 days. Nos. 2-0 silk and 2-0 plain catgut differed significantly at 28 and 42 days. No. 4-0 silk compared to No. 4-0 chromic catgut differed at 2, 4, 28, and 42 days. When the No. 4-0 silk was compared with the cotton, nylon, dacron, and teflon, statistically significant differences were apparent at all intervals except at 28 days with the cotton and 42 days with the nylon and teflon.

The mean tensile strength for 50 random samples of each suture was determined prior to implantation. The percentage of this initial tensile strength retained by each suture on the seventh and twenty-eighth postoperative days was obtained and is shown in Figure 5. On this basis, all sutures with the exception of dacron showed an appreciable change in strength which is not evident when only the changes after implantation are graphed. No. 2-0 chromic catgut retained a surprising percentage of the initial tensile strength whereas teflon lost an appreciable percentage of the initial strength.

The numerical grading obtained from the study of the tissue reaction to the sutures is shown in Figures 6 and 7. A similarity in the grade of the reaction to the nonabsorbable sutures is apparent. After the initial inflammatory reaction subsided, the histologic picture was one of rapid healing. Conversely, the inflammatory reaction was continued by the catgut sutures by the cellular response when absorption began.

Histologically, the reaction to all of the sutures after implantation for 2 days was very similar. The reaction consisted mainly of red cells, fibrin, and a few white cells, a

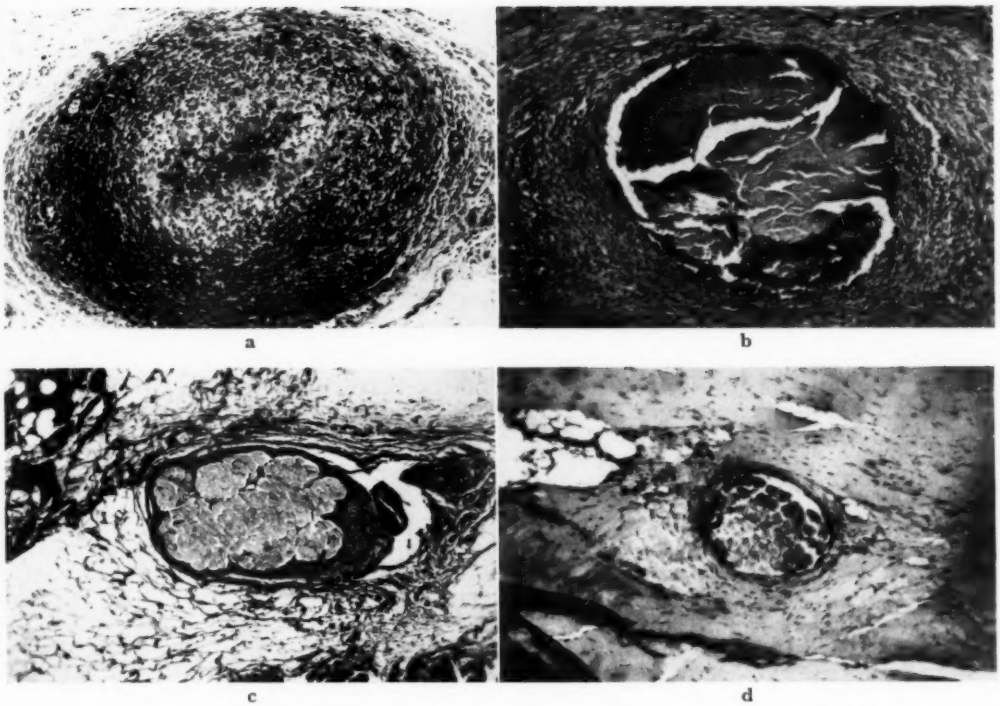

FIG. 13. Tissue reaction on forty-second postoperative day. The No. 4-0 chromic catgut in "a" and the No. 2-0 chromic catgut in "b" illustrate the variability in absorption found at the later time intervals. Silk in "c" is surrounded by mature scar. The minor reaction to teflon in "d" is notable.

degree of response which Madsen has shown may be anticipated if only a needle and suture are passed through tissue. On the fourth day, large mononuclear cells and fibroblasts predominated although in some, polymorphonuclear leucocytes and lymphocytes were still evident. On the seventh day, mature fibrous tissue made up the major portion of the reaction zone. Invariably, fibroblasts and large mononuclear cells were present as a narrow rim in the area nearest the suture. The presence and numbers of acute inflammatory cells were variable, but in general few were seen. Eosinophils were present in no particular pattern, not only on the seventh day, but at other periods. At times a marked infiltration of eosinophils was seen but with no particular type of suture.

After the seventh postoperative day, the reaction to the absorbable and nonabsorbable sutures differed appreciably. The latter uniformly showed mature fibrous tissue with an inner layer of younger fibrous tissue cells. The absorbable sutures showed the same reaction until absorption began. The time was not uniform for any suture or even uniform in an animal. When the absorption began, the acute inflammatory cells returned. Individual variations of the various sutures are noted in Figures 8 to 13.

The physical characteristics of the commonly used sutures are well known. As the teflon was a twisted suture, fraying was very noticeable. The ramie tended to swell and become sticky on sterilization. The outstanding disadvantages of all of the synthetic sutures were the tendency for a knot

to slip and the untying of the sutures in the tissues. A knot of 2 squared loops slipped invariably and of 3 squared loops, frequently. At times, even 4 squared loops would slip. The latter knot would frequently be untied by the seventh and almost always by the fourteenth postoperative day. It was estimated that 1 loop untied every 2 to 4 days.

DISCUSSION

After these studies had been partially completed, the considerable variability of the tensile strength of the wounds due to the biologic variations in the animals was appreciated. It was evident that a much more satisfactory and valid control could have been obtained by comparing the change in tensile strength of the wound with that of the intact abdominal wall of the same animal, a method which has been described by Nelson and Dennis.

The advantages and disadvantages of catgut, silk, cotton, and wire are well known and these studies have served to confirm the earlier findings of others. Ramie was similar to cotton in tissue reactivity, lost tensile strength rapidly after 2 weeks' implantation, and was difficult to handle after sterilization, all of which suggest that ramie alone would not be suitable for suture material. Dacron, nymo, and nylon stimulate little tissue reaction, maintain tensile strength well, and sterilize essentially without change, but the tendency for the knot to slip and untie is decidedly disadvantageous. The tissue reaction to teflon was the least of any of the sutures studied and the tensile strength was satisfactory. A braided suture rather than twisted would probably decrease the amount of fraying but, as with the other synthetic sutures, some alterations of the suture will be necessary so that the knot will be dependable. The favorable characteristics of teflon are so evident that further work to overcome this one disadvantage should certainly prove to be worthwhile.

SUMMARY

Plain and chromic catgut, silk, cotton, wire, nylon, ramie, nymo, dacron, and teflon were studied in animals from the standpoint of tensile strength of the sutured rectus wound, histology of this wound, tensile strength of the implanted suture loop, and grade of tissue reaction to the suture. The catgut sutures were similar to the nonabsorbable sutures until absorption began. At this time, the tissue reaction increased and the tensile strength of the suture fell rapidly. The synthetic sutures, and particularly teflon, caused little tissue reaction and maintained tensile strength well. The tendency for the knot to slip and untie was a disadvantage but the other favorable characteristics were so decisive that alterations should be sought to produce a dependable knot.

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AN ANALYSIS OF RUPTURE OF THORACIC ANEURYSMS SUBSEQUENT TO ABDOMINAL ANEURYSMECTOMY

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ALTHOUGH aneurysmal dilatation of the aorta is usually restricted to one particular location it is a reflection of generalized disease. The underlying pathologic process of atherosclerosis, calcium deposition, loss of elasticity, and dilatation of the vessel wall occurs throughout the aorta and exists in various stages of severity. In some cases multiple aneurysms are present.

It is our purpose in this article to present a clinical and pathologic analysis of 2 cases of multiple aortic aneurysms. In both cases the abdominal aneurysms were successfully treated with subsequent fatal rupture of the thoracic aneurysms ensuing. It is our postulate that these fatalities may have been precipitated by factors inherent in the treatment of the abdominal aneurysms. It is our hope that future fatalities may be prevented by an understanding of the principles presented by these cases.

MATERIAL

The following cases (Table I) are presented as illustrative of the occurrence of fatalities from ruptured thoracic aneurysms following the successful repair of abdominal aneurysms.

CASE 1. The patient was a 55 year old white male who was first admitted to Mount Sinai Hospital on April 10, 1957, because of acute lower abdominal pain of 1 day's duration. Physical examination was negative with the exception of a blood pressure of 180/120 in the right arm. Roentgenograms of the abdomen revealed a calcific aneurysm of the abdominal aorta. The pain remitted 2 days after admission and the patient was discharged. On June 28, 1957 the patient was readmitted because of recurrent abdominal pain and discharged shortly afterward.

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The patient returned to the hospital on October 1, 1957 complaining of left lateral chest pain of 3 weeks' duration. A pulsatile mass in the lower middle portion of the abdomen was now palpable. All peripheral pulses were present. Roentgenograms of the chest showed the heart to be enlarged and the thoracic aorta to be dilated distal to the arch (Fig. 1a and b).

It was decided that a staged resection of both aneurysms should be attempted. Because the plan was to use controlled extracorporeal circulation in the repair of the thoracic aneurysm, after the method of Cooley, De Bakey, and Morris, it was decided to resect the abdominal aneurysm first. This method would permit retrograde perfusion through the femoral artery and the repaired abdominal aorta at a later date. On October 18, 1957, the abdominal aneurysm was excised and replaced by a dacron prosthesis.

The variations of blood pressure during the operation are recorded in Table II. The average blood pressure during the postoperative period was 175/100. Levels as high as those recorded during the occlusion of the aorta, at the time of operation, were not seen postoperatively. On the twenty-fourth postoperative day, just prior to his planned discharge, difficulty in breathing suddenly developed associated with chest pain and the patient expired rapidly.

Postmortem examination of the thorax revealed the mediastinum to be shifted to the left. The right lung was compressed anteriorly and medially by a large extrapleural blood clot weighing 1,800 grams.

The thoracic aorta contained 2 aneurysmal dilatations (Fig. 2a and b). There was a recent rupture of the uppermost aneurysm and blood had dissected into the right thorax beneath the parietal pleura. The aneurysm began 6 centimeters distal to the origin of the left subclavian artery. It measured 13 centimeters in length, 15 centimeters in circumference, and 6 centimeters in diameter. The wall contained several secondary aneurysmal dilatations. The intima was covered by a thin film of fibrin and there was a point of recent rupture, hemorrhage, and thrombus formation in the right posterior wall of the aneurysm.

The second aneurysm was separated from the uppermost aneurysm by a 1.5 centimeter segment of aorta of average caliber. This aneurysm was 9 centi-

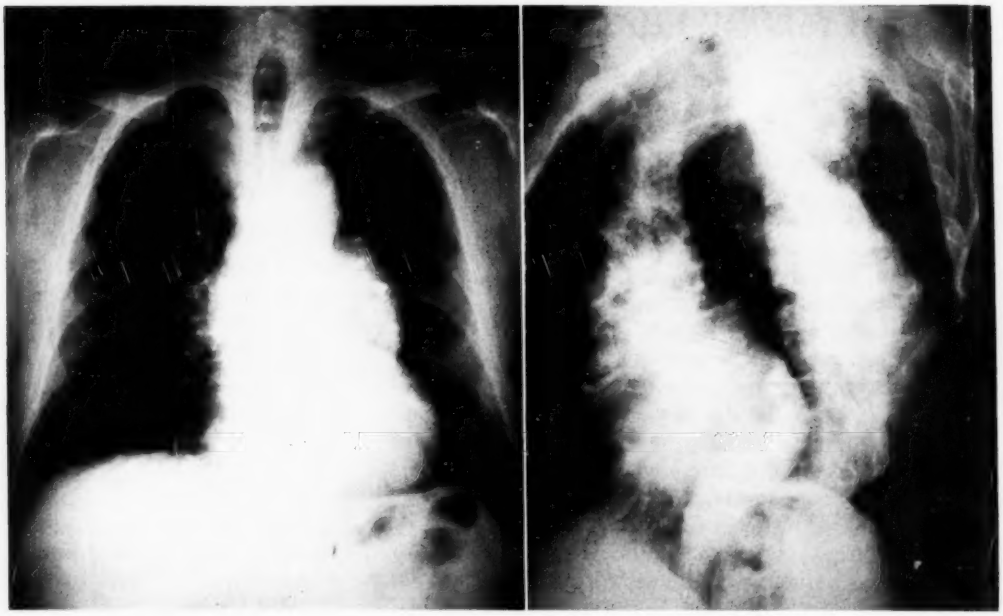

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FIG. 1. a, Roentgenograms of the chest in Case 1. a, Posteroanterior view, showing concentric enlargement of the left ventricle and aneurysmal dilatation of the thoracic aorta. b, Left anterior oblique view. The thoracic aorta is seen to be widely dilated distal to the aortic arch.

meters in length, 12 centimeters in circumference, 5.5 centimeters in diameter, and terminated approximately 5 centimeters above the origin of the renal vessels. The intima was deformed by calcific plaque formations. There were also several aneurysmal dilatations of the wall present. The intima of the ascending portion of the aorta was also markedly deformed by the presence of plaque-like depositions of cholesterol.

A major portion of the abdominal aorta was replaced by a prosthetic graft measuring 8 centimeters in length, 9 centimeters in circumference, and 4.5 centimeters in diameter (Fig. 2a and b). The graft was sutured to the proximal aorta 2 centimeters below the renal vessels and to the distal aorta 2 centimeters above the bifurcation. The anastomotic suture lines appeared well healed with no evidence of leakage, separation, or hemorrhage.

TABLE I.—SUMMARY OF CASES

Case No.	*Age of patient, yrs.*	*Operation and type of graft*	*Known duration of abdominal aneurysm*	*Known duration of thoracic aneurysm*	*Interval between operation and expiration*
1	55	Excision of abdominal aneurysm and insertion of dacron prosthetic graft	6 months	2 weeks	24 days
2	72	Excision of abdominal aneurysm and insertion of lyophilized homograft	1 month	Unsuspected	164 days

TABLE II.—THE EFFECT OF COMPLETE OCCLUSION OF THE ABDOMINAL AORTA ON BRACHIAL ARTERY PRESSURE AS RECORDED ON THE ANESTHESIA RECORD DURING OPERATION

Case No.	*Blood pressure before occlusion*	*Mm.Hg 5 min. after occlusion*	*20 min. after occlusion*	*Prior to release of clamp*	*Immediately following release of clamp*
1	190/145	230/165	235/165	210/150	150/100
2	180/120	90/60	205/130	200/140	130/85
3*	150/90	180/100	200/115	230/120	145/100

*Values taken from record of a 69 year old male who underwent an excision of an abdominal aneurysm. Included in table as supplemental information.

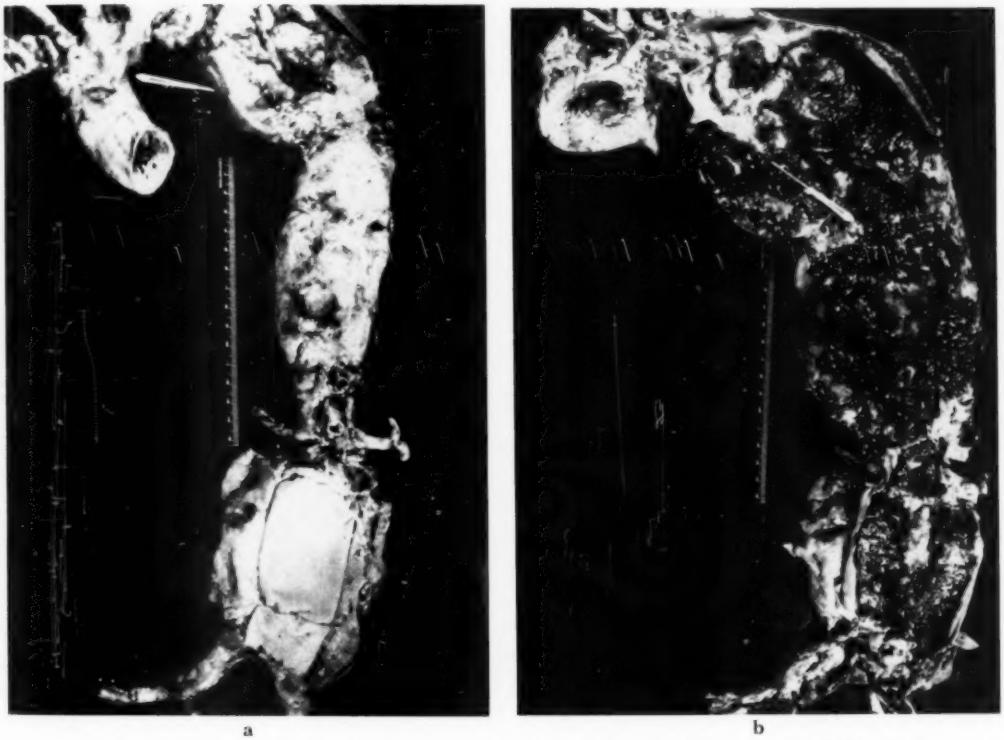

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FIG. 2. Case 1. a, Anterior view of the external surface of the aorta. Two aneurysmal dilatations of the thoracic aorta are present. Note the probe in the area of fatal perforation. A dacron prosthetic graft is present below the renal vessels. b, Internal surface of host aorta and dacron graft. The probe is placed through the area of perforation in the upper aneurysm.

The inner surface of the graft was lined by a continuous coat of fibrin containing grossly visible lines of Zahn (Fig. 3a and b). This newly formed inner lining measured 0.3 centimeter in thickness, and extended for a short distance into the segments of aorta both proximal and distal to the graft.

On microscopic examination there was severe atherosclerosis of the intimal zone in all regions of the aorta. Focal arteriosclerotic changes were seen in the media. There was marked depletion of the elastic tissue.

Sections from the aneurysmal portions of the aorta show many areas of old and recent thrombus formation with severe arteriosclerotic changes (Fig. 4). A section of the upper thoracic aneurysm in the region of the rupture shows destruction of the wall with many areas of recent hemorrhage. The clot present on the inner surface of the graft is seen to be composed of fibrin arranged in a laminated pattern alternating with clotted elements of the circulating blood (Fig. 3b).

CASE 2. The patient was a 72 year old white male who was admitted to the hospital because of abdominal pain of 3 months' duration. Physical examination showed a blood pressure of 170/100 and a pulse of 84. A large pulsating mass was palpable in mid abdomen.

A roentgenogram of the chest (Fig. 5) showed the heart to be enlarged to the left. Overlying the midline and extending predominantly toward the right was a fairly well demarcated homogeneous density seen through the cardiac silhouette. This was interpreted to represent an elongated tortuous aorta.

On September 24, 1957, the abdominal aortic aneurysm was resected below the renal vessels and a lyophilized bifurcation homograft inserted. Changes in blood pressure occurring during the operative procedure are recorded in Table II. On October 17, 1957, the patient left the hospital after a benign postoperative course. The patient's blood pressure on discharge from the hospital was 160/100.

The patient was well until March 5, 1958, at which time severe abdominal and back pain developed. He was admitted to the hospital in a state of shock with a blood pressure of 75/50 and a pulse rate of 100.

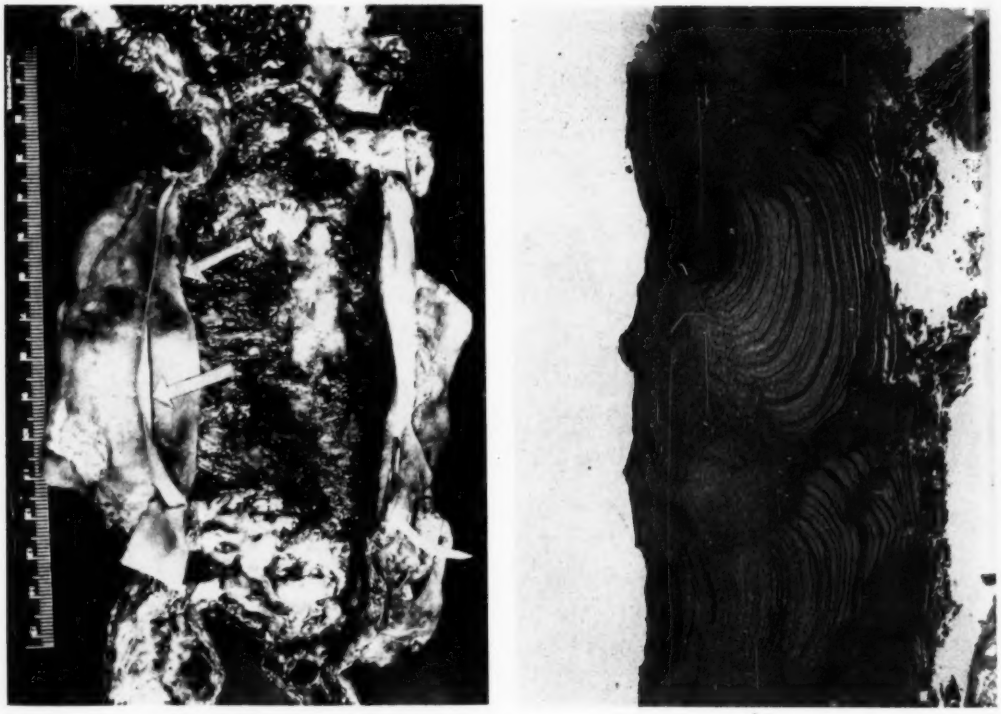

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FIG. 3. Case 1. a, Internal surface of dacron graft. Anastomotic suture lines appear well healed with no evidence of disruption. Upper arrow indicates a distinct layer of fibrin, 0.3 centimeter in thickness, lining the inner surface of the graft. The lower arrow indicates the dacron edge. b, Photomicrograph of the fibrin clot lining the dacron graft. Note the laminated pattern of deposition of fibrin alternating with elements of the circulating blood stream.

An exploratory laparotomy was immediately performed and revealed the absence of free blood in the peritoneal cavity. The homograft was noted to pulsate normally with no evidence of suture line leakage or graft rupture. A diagnosis of rupture of a thoracic aneurysm was made. Because of the rapid deterioration of the patient's condition, it was deemed inadvisable to enter the thoracic cavity. The patient expired several hours later.

At postmortem examination there were approximately 2,000 cubic centimeters of serosanguineous fluid and several large blood clots in the right hemithorax. The posterior mediastinum contained 1,500 cubic centimeters of clotted blood. The thoracic aorta, above the level of the diaphragm, presented a large saccular aneurysmal dilatation about 7 inches in diameter. The wall was severely atherosclerotic and composed of soft fragmented atheromatous material mixed with clotted blood (Fig. 6a). There was a perforation present in the right margin of the aneurysm.

The aortic homograft, which extended from 5 centimeters below the renal vessels to 2 centimeters below the aortic bifurcation, was intact. The graft measured 6½ centimeters in length and 3½ centimeters in circumference. The anastomotic sites appeared well healed. The intimal surface appeared smooth (Fig. 6b). There was no dilatation of the graft. The host aorta proximal to the graft was 6 centimeters in circumference. The wall was atherosclerotic and thin.

On microscopic examination sections of the graft revealed a pseudointima, acellular media, and mild round cell infiltration of the adventitia. There were foreign body giant cells present in the adventitia. The elastic fibers of the graft appeared well preserved with the exception of 1 area of disruption and fragmentation of these fibers in the media. A small amount of calcium was present in 1 area of the media of the graft.

The host aorta was markedly abnormal with loss of the normal vessel architecture. There was severe

FIG. 4.

FIG. 4. Case 1. Photomicrograph of a segment of the wall of the thoracic aneurysm. The intimal aspect contains an old thrombus. The arrow indicates cholesterol clefts in the intimal and medial layers. There is thinning of the media. Hematoxylin-eosin stain, ×19.

FIG. 5.

FIG. 5. Case 2. Roentgenogram of chest. Postero-anterior view, showing rounding of the left lateral cardiac border. The thoracic aorta appears widened as seen through the cardiac silhouette. The arrow points to a round density in the right paravertebral region near the cardiophrenic angle.

atherosclerosis of the intimal and medial layers (Fig. 7a). There was marked depletion, fragmentation, and disruption of the elastic tissue noted (Fig. 7b).

DISCUSSION

The cases presented are examples of generalized disease of the aorta as evidenced by the presence of multiple aneurysmal dilatations. In both cases, the lowermost aneurysm was treated first with fatal rupture of the most proximal aneurysm occurring relatively soon afterward. While one cannot definitely state that these events occurred as cause and effect, the supposition is a strong one and presents several worthwhile considerations (See Table II).

In the surgical repair of abdominal aortic aneurysms, the aorta proximal to the aneurysm is completely occluded for a significant period of time. What effect does this have on the proximal intra-aortic pressure? Studies have been done which show that aortic occlusion in man, reciprocally, but not equally, affects the blood pressure proximal and distal to the point of occlusion. Fitzpatrick and co-workers recorded simultaneously the brachial artery and femoral artery pressures during occlusion of the aorta in repair of arteriosclerotic abdominal aneurysms. With the onset of aortic compression, the brachial artery pressure rises and the femoral artery pressure falls.

In the cases presented in Table II, it is evident that the blood pressure was significantly increased following complete occlusion of the aorta. This pressure was sustained during the period of occlusion required and was seen to drop immediately

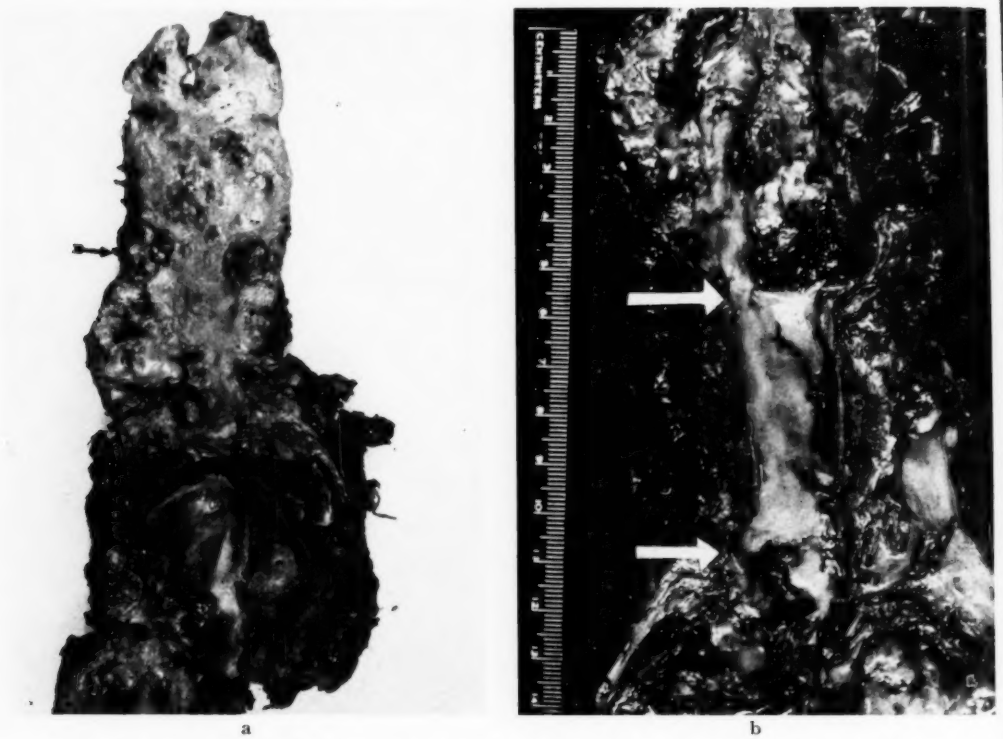

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FIG. 6. Case 2. a, Intimal surface of the thoracic aorta. Note severe atherosclerotic changes of the entire thoracic segment. The lower arrow indicates the area of perforation in the aneurysmal dilatation. The upper arrow indicates the nonaneurysmal segment of the aorta. b, Intimal aspect of the abdominal aorta (opened posteriorly in situ). The smooth intimal surface of the homograft is noted between the arrows. The proximal host aorta is composed of soft atheromatous material.

following the release of the aortic clamp. It must also be considered that the actual intra-aortic pressure proximal to the point of occlusion is higher than the mean brachial artery values, as shown by Kroeker and Wood. These distortions in pressure created by impairment to normal aortic blood flow can also be observed clinically in cases of coarctation of the aorta.

The next point of consideration is the effect of the increased blood pressure on the wall of the proximal aorta. The different characteristics of the thoracic and abdominal aorta have been studied. Bader has shown by means of pressure volume studies that the thoracic aorta, at a given pressure, will expand its volume capacity to a greater degree than the abdominal aorta. The greater amount of elastic tissue and collagen in the thoracic aorta accounts for this difference. Age and degenerative changes also affect the elastic distensibility of the aorta.

While the normal aorta with good elastic fibers in the media is able to withstand the blood pressure alterations described previously, the diseased aorta may not be able to withstand the increased pressure. As seen in the cases presented, the thin walls of the thoracic aneurysms contain atheromatous plaques, areas of degeneration and necrosis, and fragmentation and depletion of the elastic fibers. If the increased intra-aortic blood pressure, resultant from aortic occlusion during surgical repair of the abdominal

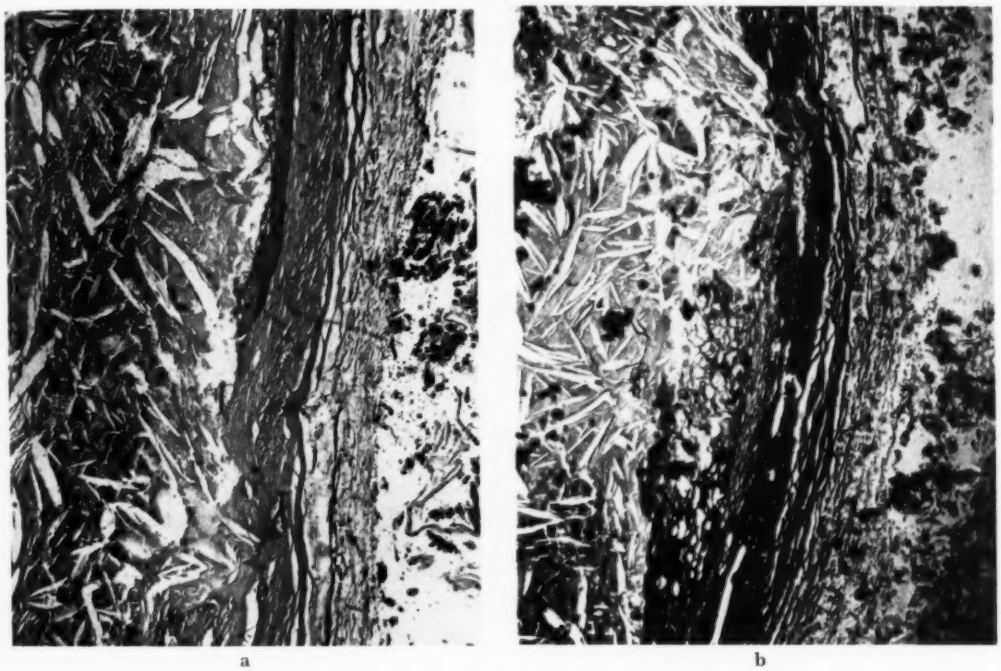

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FIG. 7. Case 2. Photomicrographs of host aorta. a, Severe atherosclerotic changes and complete loss of normal vessel architecture are shown. Cholesterol clefts are seen in the intimal and medial layers of the aortic wall. b, The elastic fibers of the media are depleted. The remaining fibers are fragmented and disrupted by cholesterol deposits. Weigert-Van Giesen stain, ×53.

aneurysm, exerts a stress on the proximal vessel wall causing further fragmentation of the elastica, cracking of the atheromatous plaques, or beginning dissection of the necrotic wall, the repair of the distal aneurysm may become an added factor in initiating the onset of the proximal aneurysm rupture.

It would next be a logical conclusion to consider the importance of treating cases of multiple aneurysmal dilatation by repairing the most proximal aneurysm first. This method would avoid the production of deleterious effects upon the remaining aortic disease. If the situation should necessitate repair of the lowermost aneurysm first, an attempt should be made to counteract the increased pressure by utilizing arfonad before application of the occluding clamps to maintain the pressure at desired levels.

Another approach would be the one stage resection of all the aneurysms with the aid of hypothermia or pump oxygenators. Though this would be a formidable procedure if it were performed in the cases presented, De Bakey has successfully resected an extensive aneurysm of the lower thoracic and upper abdominal aorta.

SUMMARY AND CONCLUSIONS

1. Multiple aneurysms of the aorta exist and are a reflection of a generalized disease process affecting the aorta.

2. In cases in which one aneurysm is demonstrated, the existence of other aneurysmal dilatations should be considered.

3. Repair of the distal aneurysm increases intra-aortic blood pressure and may place sufficient stress on the wall of the proximal aneurysm to initiate pathologic changes leading to subsequent fatal rupture.

4. It is suggested that in the event of staged repair of multiple aortic aneurysms, the most proximal aneurysm should be repaired first.

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A MICROSCOPIC STUDY OF THE GROWTH OF LEIOMYOMAS OF THE UTERUS DURING PREGNANCY

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THE CONSENSUS is that leiomyomas of the uterus grow during pregnancy. Randall and Odell in 1943 presented evidence that this is not true. Emge had previously doubted that they showed true growth during pregnancy. In 1952 Parks and Barter expressed the same opinion as did MacLeod and Read in 1955.

The claimed "growth" of these tumors during pregnancy is usually attributed to one or more of three mechanisms:

1. Apparent increase in palpable surface area without true increase in mass. Myomas tend to maintain their shape (with some flattening) and thus become more prominent as the uterine wall thins out late in pregnancy. The enlarging uterus, moreover, tends to pull low lying leiomyomas upward out of the pelvis in the mid and last trimester of pregnancy and during labor. Thus it is seen that an apparent increase in the bulk of a uterine leiomyoma, as determined by palpation, may be caused by several factors acting alone or together: (a) a thinning of the uterine wall found mainly in the third trimester causing a more superficial location of intramural leiomyomas, (b) a wandering or relocation upward out of the pelvis caused by enlargement of the uterus during pregnancy and by formation of the lower uterine segment, (c) an increase in palpable surface area through flattening by pressure, retraction, and separation of contiguous tumors.

2. Swelling due to degenerative changes. Some authors believe that venous stasis, edema, and hyaline degeneration become more evident with the advancement of pregnancy and these factors could explain, at least partially, the "enlargement" of leiomyomas during pregnancy. The criteria for the microscopic diagnosis of edema, however, are open to question especially in the case of leiomyomas. It is usually said that during pregnancy the individual muscle cells of the leiomyoma and myometrium appear swollen and the nuclei vesicular. It has also been claimed, however, that true edema is uncommon and that most cases so described are actually examples of liquefaction following hyaline degeneration, the differentiation being made on the basis of the lower albumin content of true edema fluid. Randall and Odell have claimed that edema from severe degenerative change is not present in the absence of symptoms. Emge has stated that venous stasis and edema do not progress materially after the seventh month although other degenerative changes may continue.

Even in the nonpregnant uterus leiomyomas are known to undergo a variety of degenerative changes: hyalinization; necrosis; and mucoid, calcific, fatty, and carneous or red degeneration. According to Campbell, 50 to 75 per cent of leiomyomas removed from pregnant women showed degenerative changes in comparison to 7 to 10 per cent in those removed from nonpregnant women. This increased incidence of degenerative change is most often explained on the basis of poor vascular supply; i.e., the growth of the leiomyoma outstrips the vascular supply or more reasonably there is a torsion of the vessels entering from the periphery. This torsion occurs with the thinning of the uterine wall and the wander-

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TABLE I.—PER CENT SHOWING MODERATE OR SEVERE DEGENERATIVE CHANGE

Tissue group	*No. in series*	*Extracellular edema, per cent*	*Intracellular edema, per cent*	*Fibrosis, per cent*	*Hyalinization, per cent*	*Necrosis, per cent*
Leiomyoma						
Nonpregnant	22	45	55	45	27	9
Early pregnancy	14	50	36	20	36	0
Late pregnancy	16	38	38	75	50	30
Myometrium						
Nonpregnant	22	22	18	0	0	0
Early pregnancy	14	43	14	0	0	0
Late pregnancy	16	38	25	0	0	0

ing and retraction mentioned as a cause of apparent growth. Because the increased myometrial blood flow does not reach the leiomyoma, the resultant slowly developing anoxia eventuates in a proliferation of the more hardy connective tissue elements at the expense of the muscle cell. If the process continues, other forms of degenerative change, such as hyalinization, may occur. If the anoxia is more acute in onset, necrosis may result.

3. Hypertrophy and hyperplasia of smooth muscle and connective tissue. It is well known that myometrial muscle cells undergo hypertrophy during pregnancy that is reflected in a greater area of the cell as seen microscopically. It has long been assumed that leiomyoma muscle cells undergo hypertrophy proportional to that of the myometrial cells in response to either direct stimulation from the increased amount of various hormones, especially estrogen, or indirect stimulation from the increased blood supply. Randall and Odell, however, in a study of 17 leiomyomas remarked on the evident lack of hypertrophic response of the tumor's muscle cells during pregnancy; i.e., the size of the leiomyoma muscle cells did not keep pace with the increased size of the myometrial cells.

THE PRESENT STUDY

For the present study a review of the files of the laboratory of Obstetrics and Gynecology of Northwestern University Medical School was made for microscopic sections of pregnant uteri containing leiomyomas. These slides had been prepared in this laboratory from surgical specimens obtained since 1937 at Passavant Memorial Hospital and since 1946 at Chicago Wesley Memorial Hospital. Fixation in most instances was by use of formalin for varying periods while the specimen was at the hospital and transferred to Bouin's solution for about 1 day after arrival at the laboratory. All of the slides were stained with hematoxylin-eosin and the Milligan trichrome stain which differentiates muscular tissue from collagenous connective tissue; a number of slides were also stained with the periodic acid Schiff technique.

Thirty slides containing sections of myometrium and leiomyoma side by side in the same block were studied in detail. In all cases, the duration of pregnancy was determined by history or morphologic evidences such as length of the embryo or fetus and development stage of placental villi. Of these, 14 specimens were from women in the first trimester of pregnancy and 16 from the third trimester. Only 2 specimens were found from the second trimester and these were not included in this study. A control group of 22 specimens of leiomyomas from nonpregnant uteri was taken mainly from the surgical specimens received during 1956 and 1957. These were similarly fixed and stained.

All of the leiomyomas studied were of comparatively small size, the range being 1.1 to 1.7 centimeters for the mean diameter of tumors in the three groups. This, of course, is an artificially small-size range but was judged necessary because only those slides were considered satisfactory which showed both tumor and normal myometrium side by side.

TABLE II.—SUBJECTIVE IMPRESSION OF RELATIVE SIZE OF MYOMETRIAL AND LEIOMYOMA CELLS IN THE THREE GROUPS PER CENT OF SPECIMENS SHOWING CELLS OF ONE TISSUE PREDOMINANTLY LARGER THAN THE CELLS OF THE OTHER TISSUE

		Leiomyoma cells larger than myometrial cells, per cent		*No appreciable difference in size,* per cent		*Myometrial cells larger than leiomyoma cells,* per cent	
Group	*No. in group*	*E.J.L.*	*R.R.G.*	*E.J.L.*	*R.R.G.*	*E.J.L.*	*R.R.G.*
Nonpregnant	22	55	0	40	100	5	0
Early pregnancy	14	15	0	62	85	23	15
Late pregnancy	16	13	0	13	6	75	94

METHODS AND RESULTS

Degenerative changes. In this study, an attempt was made to compare the amount of degenerative change in a semiquantitative manner. For the purpose of tabulation those tumors showing minimal or no evidence of degenerative change were grouped together and compared to those with moderate or marked degenerative change. In the case of hyalinization and necrosis, a tumor was considered to be in the moderate or marked group if the hyalinized or necrotic tissue occupied more than one-tenth of a low power field in the smallest tumors. In the case of fibrosis, a moderate to marked designation was given to those tumors in which the area occupied by fibrous connective tissue was equal to or greater than the area occupied by smooth muscle. The degree of extracellular clear space or the nonstaining area between fibers which we labelled "edema" and intracellular clear space or the vacuoles and nonstaining intracellular areas also labelled "edema" were assigned arbitrary subjective comparative classes impossible of accurate definition. The small size of the tumors studied as well as the small number of cases in this series prevent any conclusions regarding the relative prevalence of the most severe degrees of degenerative change since only a few examples of these were found but it was observed that they were not confined to any one group.

No correlation was seen between age of patient, number of previous pregnancies, when known, or size of the leiomyoma within this small range of diameters, and the amount of degenerative change present.

It may be seen from Table I that about one-third to one-half of the specimens in each of the nonpregnant, early or first trimester of pregnancy, and late or third trimester of pregnancy groups had appreciable amounts of the nonstaining clear spaces both intracellularly and extracellularly and that this finding was usually more prominent in the tumor than in the myometrium. The figures were submitted to the chi square test and it was found that there were no significant differences among the three groups at the 95 per cent level of probability.

On further inspection of Table I it may be seen that there was only a slight increase in the prevalence of moderate or marked hyalinization in leiomyomas from uteri in late pregnancy, as compared to those from nonpregnant uteri. However, there was a more marked increase in the prevalence of fibrosis and necrosis in tumors during late pregnancy. The differences between the two groups were significant at the 95 per cent level of probability. The incidence of necrosis of appreciable degree was not as great as in the figures previously quoted by Campbell, possibly because the present series was composed only of small tumors. The apparent decrease in the prevalence of degenerative changes during early pregnancy was not statistically significant but, as we shall discuss later, could be explained on the basis of blood supply variations.

Hypertrophy and hyperplasia. Table II is a tabulation of the subjective impressions of the relative size of myometrial and leiomyoma cells in the three groups as made independently by the two authors. It is obvious that subjective impressions are very subjective and not too suitable for detailed analysis. The important point, however, is

FIG. 1. Nonpregnant patient. Leiomyoma to right and myometrium to left. There is no appreciable difference in the muscle fibers. ×68.

that in the specimens obtained during late pregnancy the majority were judged by both authors to have myometrial cells larger than the leiomyoma cells, whereas fewer than one-quarter of the specimens from early pregnancies and few or none of those from the nonpregnant group showed this difference in size of the cells. These findings support the previous observation of Randall and Odell that the hypertrophy of the myometrial cells outstrips any possible hypertrophy of leiomyoma cells.

The second method of comparison was more time-consuming, was more limited, but probably was somewhat more accurate. In 18 of the specimens, the diameters of the nuclei and cells were measured by the use of the ocular micrometer. These slides were stained either with Milligan trichrome or with the McManus modification of the periodic acid Schiff stain. The cellular boundary was accurately defined by either technique but especially by the periodic acid Schiff stain because of the presence of a periodic acid Schiff positive substance surrounding each smooth muscle cell in both the myometrium and the leiomyoma. Because of the spindle shape of the smooth muscle cell, it was rarely present from end to end in one section. Therefore, the widest diameters seen in longitudinal section were measured. This technique, of course, minimizes differences between the size of cells.

TABLE III.—OBJECTIVE MEASUREMENT OF RELATIVE SIZE OF MYOMETRIAL AND LEIOMYOMA CELLS

	Myometrium, units	*Leiomyoma, units*
Nucleus		
Nonpregnant	2.3	2.6
Early pregnancy	2.4	2.9
Late pregnancy	2.8	2.9
Cell		
Nonpregnant	3.8	3.8
Early pregnancy	3.7	4.6**
Late pregnancy	5.4*	4.5

Mean diameters determined by 50 measurements in each of 4 to 6 specimens per group expressed in ocular micrometer units (1 unit = 1.2 microns). Coefficient of variation of 4.3 to 15.4 per cent.
*Significantly larger than leiomyoma cell in late pregnancy.
**Significantly larger than in nonpregnant leiomyomas.

In each specimen an attempt was made to measure the cellular and nuclear boundaries of all cells which could be brought into sharp focus in 6 or 8 areas in which the smooth muscle fibers had a fairly constant direction of flow. Fifty nuclei and cells in each of the 4 to 6 leiomyomas in each group and 50 nuclei and cells in the adjacent myometrium were measured giving a total of about 3,000 separate readings. At a magnification of 430 the nucleus occupied from 1 to 6½ micrometer units and the cell from 2 to 7 units. One micrometer unit was the equivalent at this magnification of 1.2 microns or 0.0012 millimeter. The size of the nucleus and cell in the individual sections varied within rather narrow limits for the most part. The coefficient of variation of the mean diameters for each group of 4 to 6 specimens measured was usually below 10 per cent although in 1 group it was 15 per cent.

The data are presented in Table III and show that the mean diameters of the nuclei in myometrial and tumor tissue were approximately equal to each other. For both tissues, no significant difference was noted among the three groups.

Comparing cellular diameters in the nonpregnant group, the cells of the leiomyoma had approximately the same mean diameter as the cells of the myometrium. In specimens from the first trimester (early pregnancy), the mean cellular diameter of the myometrium was approximately the

same as that in the nonpregnant group. In these specimens from early pregnancy, however, the mean cellular diameter of the leiomyoma tissue was appreciably larger than that of the same tissue in the nonpregnant group (and also appreciably larger than the mean diameter of the myometrial cells in the early pregnancy group).

These findings are not wholly in agreement with our subjective impressions (Table II) that in the majority of the specimens from the early pregnancy group, the cellular diameter of the tumor cells was approximately equal to that of the myometrial cells.

These values shown in Table III were submitted to statistical analysis. The ratio was within acceptable limits for a sample this size at the 95 per cent level of probability.

In late pregnancy there was a reversal of the relative size of the two cells; the mean diameter of the leiomyoma cell remained approximately the same as in early pregnancy, but the mean diameter of the myometrial cell increased by 50 per cent. Again the increase was sufficient to be statistically significant at the 95 per cent level; the difference between the diameters of the myometrial cells and the leiomyoma cells was also significant although opposite in direction from that observed in the group from early pregnancy.

DISCUSSION

Although nuclear size remained relatively constant, cellular size in the leiomyoma increased during early pregnancy and then remained constant. In the myometrium, however, the increase in cellular diameter lagged behind at first and later significantly surpassed that of the leiomyoma. Thus the leiomyoma cell was larger in the early pregnancy group than in the nonpregnant group. In fact in the early pregnancy group the leiomyoma cell was larger than the myometrial cell. In the late pregnancy group, however, the myometrial cell was significantly larger than the leiomyoma cell.

FIG. 2. First trimester of pregnancy. There is no appreciable difference in this photomicrograph between size of the muscle fibers in the leiomyoma to the right and the adjacent myometrium on the left. ×68.

The leiomyoma cell did not undergo the great hypertrophy of later pregnancy as did the myometrial cell!

It is well to recall that in this study we have measured the increase in size from only one dimension. The greatest increase occurs in the length of the muscle cell, approximately tenfold according to Greenhill and Eastman. Thus, our findings minimize the changes that take place.

Although by the methods used in this study no change in myometrial nuclear size was detected during pregnancy, by

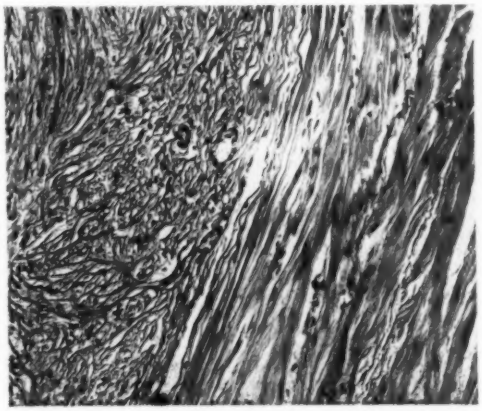

FIG. 3. Third trimester of pregnancy. The muscle fibers of the leiomyoma on the right are smaller than those of the adjacent myometrium on the left. ×106.

more sensitive methods Salvatore demonstrated that there was an increase in volume of the nuclei of the myometrium during pregnancy.

No conclusions may be drawn concerning the occurrence of hyperplasia. We prefer to interpret the increase in fibrous tissue in tumors obtained during pregnancy as a relative increase and a reflection of degeneration, rather than hyperplasia. Mitotic figures were conspicuous by their absence in both leiomyomas and myometrium.

The prevalence of degenerative change was higher in the late pregnancy group than in the nonpregnant group and especially higher than in the early pregnancy group. Assuming that these degenerative changes were responses to anoxia, one could postulate that the blood supply to the leiomyomas is poorest during late pregnancy and possibly best during early pregnancy. Our data are not sufficient to show that this is a statistically valid conclusion.

Gillespie has demonstrated that during the first half of pregnancy there is a rapid increase in uterine weight which is presumptive evidence of actual growth since myometrial thickness is maintained although the uterus is becoming increasingly larger. We are unable to explain why this is not reflected in an increase in cellular diameter in our findings; certainly the increased mass is not solely the result of hyperplasia. During the second half of pregnancy, according to Gillespie, the increase in weight is much less and the myometrium becomes progressively thinner, and thus, it is presumed that uterine growth slows or ceases. Again we are unable to reconcile this conclusion with our finding that cellular hypertrophy, if this is what is shown by increase of diameter, occurs in late pregnancy rather than early pregnancy.

Sampson and Faulkner have shown that the arterial supply of leiomyomas is from one or more nutrient arteries entering from the periphery and encircling the tumor. It has been postulated that the higher incidence of degenerative changes found during pregnancy is caused by a torsion of or traction on these nutrient vessels as the tumor rotates within its pseudocapsule of condensed myometrium. This twisting is theoretically brought about by the passive thinning and stretching of the uterine wall as well as by active contraction of its fibers and retraction upward from the lower uterine segment; i.e., the same factors which are held to cause an apparent increase in the palpable surface of the tumors.

It is possible that during early pregnancy when the thickness of the uterine wall is maintained and before thinning, stretching, and retraction have occurred the blood supply of the leiomyoma, along with that of other pelvic structures, is increased sufficiently to permit hypertrophy of the fibers and to prevent anoxic degeneration. It is also possible that later in pregnancy the blood supply is embarrassed by the action of these factors to such an extent that further hypertrophy ceases and anoxic degeneration begins.

We do not propose this as the final answer to the question of the behavior of leiomyomas in pregnancy. We believe, however, that it better explains the response noted than does the estrogen stimulation theory. According to this latter theory, greatest stimulation would occur during the third trimester when the highest levels of estrogen are attained, whereas the slight hypertrophy of the tumor cells which we noted occurred during the first trimester before any great elevation of estrogen had occurred.

If very much true growth of leiomyomas does occur during pregnancy, we believe that little of it may be accounted for on the basis of hypertrophy of the smooth muscle fibers. Perhaps in larger and especially in symptomatic tumors, swelling may occur from acute or chronic anoxic degeneration. In small tumors, such as those studied, this factor, although present in a significantly greater percentage of the specimens from pregnant than nonpregnant women, would probably not be of great importance in producing alterations of size.

To us, then, it seems most reasonable that the major factors in palpable "growth" of leiomyomas in pregnancy are more apparent than real: a thinning of the uterine wall, wandering upward out of the pelvis by the tumors, flattening by pressure and separation of contiguous tumors, and failure on the part of the observer to detect their existence and rate of growth prior to pregnancy.

SUMMARY

An analysis of the microscopic characteristics of 30 small leiomyomas from pregnant uteri and 22 from nonpregnant uteri was made. A significant increase in the incidence of necrosis, hyalinization, and the amount of fibrous tissue stroma was noted in the specimens from third trimester pregnancies in comparison with those from either first trimester pregnancies or from nonpregnant patients.

A tabulation was made of the subjective impression of the relative size of the cells of the leiomyoma and the myometrium. It was thought that, in few of the specimens from the nonpregnant patients but in most of the specimens from patients in the third trimester of pregnancy, the myometrial cells were larger than the cells of the leiomyoma.

In 4 to 6 specimens from the nonpregnant, first trimester, and third trimester groups, the diameters of the nuclei and cells were measured with the ocular micrometer at a magnification of 430. It was found that nuclear size did not increase sufficiently to be detected by this method. Cellular size in the leiomyoma increased during early pregnancy and then remained fairly constant. In the myometrium, however, the increase in cellular diameter lagged behind during the first trimester but in the third trimester significantly surpassed the increase in diameter of the leiomyoma cells.

It is believed that these findings may be more easily explained by changes in blood flow reaching the tumor than on the basis of changes in estrogen titers. Since uterine wall thickness is maintained during the first half of pregnancy, the blood supply to the tumors should be maintained or increased in proportion to that of the myometrium. In the second half of pregnancy, the uterine wall is thinned and there is then postulated a torsion of the nutrient vessels reaching the tumor. Leiomyomas, therefore, do not partake in the increased blood flow available to the myometrium. Correlating the changes in cellular diameter with this suggested change in blood flow, we can understand why the leiomyoma cell hypertrophies during the first half of pregnancy and why the incidence of anoxic degenerative change is less during the first half of pregnancy than it is during the second half of pregnancy.

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WERTHEIM HYSTERECTOMY IN THE TREATMENT OF ENDOMETRIAL CARCINOMA

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IN THE PAST 20 YEARS it has become common custom to treat cancer of the endometrium in one of two ways. (1) The elderly patient who is a poor surgical risk because of her obesity, diabetes, and hypertension has been treated definitively by some form of radiation. In most instances, this has been intracavitary radiation employing a wide variety of intrauterine applicators. At times the intrauterine radiation has been supplemented by external roentgen ray therapy. Depending upon the extent of the disease, the general condition of the patient, the radiation equipment available, and the experience of the gynecologist applying the radium, 5 year results ranging from 40 to 60 per cent have been reported. There is little reason to wish to modify this form of treatment for this group. (2) The patient who was regarded as a good surgical risk, with the disease confined to the endometrial cavity, customarily received intrauterine radium as a preliminary step to the final surgical removal of the entire uterus, tubes and ovaries, and a section of the vaginal apex. In past years the time interval between the application of radium and the surgical removal of the uterus was placed at 6 weeks. In recent years there has been a tendency to shorten this interval to a week or 10 days. In many clinics, radium is applied to the apex of the vagina or x-ray therapy is given to cut down the incidence of metastases at the apex of the vagina. The 5 year end results reported average between 65 and 70 per cent. A number of clinics have reported 5 year salvage in the range of 80 per cent, but the general average varies between 65 and 70 per cent.

There has been considerable interest among pathologists in the amount of residual carcinoma found in the excised uterus after preliminary radiation. The amount of cancer remaining will depend in part upon the nature of the original growth. If the adenocarcinoma is confined to the endometrium alone, intracavitary radium may well destroy it and no remnants will be found. Unfortunately, there is no way of knowing the manner of spread within the uterine cavity until after the uterus has been removed. Several large series reported show that more than 50 per cent of the postradiated hysterectomy specimens contain pathologic evidence of persistent carcinoma.

The persistence of carcinoma after a preliminary course of radium has aroused some doubt of its value in the treatment of endometrial carcinoma. There is a tendency to go back to total hysterectomy, bilateral salpingo-oophorectomy with a wider resection of the upper vaginal canal, and to give up the use of intracavitary radium. Undoubtedly, such an operation will be effective provided the primary disease is confined to the endometrium and no myometrial invasion has taken place. Again, it is unfortunately a fact that we cannot know whether or not this is true until the uterus has been removed.

Many cases of endometrial carcinoma have myometrial invasion. It therefore seems illogical to offer an operation that is little more than one would do for a benign fibroid to a patient with invasive cancer. It is our

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belief, furthermore, that the recurrences occasionally found in the vaginal canal after operation are due to retrograde lymphatic dissemination rather than implantation at the time of operation. Customarily, these metastases appear beneath the vaginal epithelium on the anterior wall. We have seen it appear alongside the external urethral opening as late as 7 years.

In view of the renewed interest in radical dissection of the pelvic lymphatics for cervical cancer created by Meigs (9), Brunschwig (1) and others, we have elected to employ the Wertheim type of hysterectomy and pelvic node dissection in the treatment of endometrial carcinoma.

This report, based on 62 cases in which treatment consisted of the Wertheim hysterectomy, is presented as a critical study of the many factors underlying the management of endometrial carcinoma by a radical surgical approach.

MATERIAL

Between 1946 and 1956 a total of 62 unselected patients with diagnoses of carcinoma of the endometrium underwent a radical Wertheim hysterectomy. Of these, only 50 were subjected to bilateral pelvic lymph node dissection. Ten patients who had received previous irradiation are listed as a separate group.

The average age was 57 years, the youngest 34 and the oldest 79 years. It is generally stated that 75 per cent of the cases of endometrial carcinoma occur after the age of 50. Characteristically, 82.3 per cent of the patients in this study were between 50 and 79 years of age while only 17.7 per cent were under 50 years of age. There was 1 patient aged 34 years, while 10 were between 40 and 50 years old. The ages of 25 patients, or 40 per cent, ranged between 60 and 79 years.

All patients had a positive microscopic diagnosis either at the time of operation or by preliminary biopsy. In no case was the diagnosis of carcinoma in situ or hyperplasia made.

TABLE I.—TYPES OF PATHOLOGY IN 62 CASES

Pathology	*Primary group*	*Radiated group*
Adenocarcinoma	44	8
Adenoacanthoma	7	2
Carcinosarcoma	1	0
Total	52	10

TABLE II.—LESION LIMITED TO THE ENDOMETRIUM

	No. of cases
Untreated group	21
Irradiated group	4
Total	25*

*40 per cent of 62 specimens.

SURGICAL PATHOLOGY

The type of pathologic conditions noted in this series is listed in Table I. Adenocarcinoma was the most frequent type of malignant tumor present in 52 cases. Adenoacanthoma was diagnosed in 9 cases while carcinosarcoma occurred in 1. Of 52 patients with adenocarcinoma, 44 were previously untreated, while 8 had received previous irradiation. One patient had undergone previous irradiation followed by a subtotal hysterectomy. Of the 10 patients with previous irradiation, 6 showed residual disease in the surgical specimen. Lymph nodes positive for cancer were encountered in 4 of the 50 patients subjected to bilateral pelvic lymphadenectomy. If myometrial spread alone is considered, lymph nodes were positive in 4 out of 37 instances of myometrial invasion, or 11 per cent.

MYOMETRIAL INVASION

It is generally believed that invasion in carcinoma of the endometrium is a comparatively late development. Hertig and Sommers have shown that an intramucosal lesion may precede invasive cancer by years. Once the malignant cells have broken through the basal stratum, however, the rapidity of their spread through myometrium, lymphatics, and adjacent structures is unpredictable. Javert (6) reported an incidence of 82 per cent of myometrial invasion in 229 surgically removed uteri.

In the present series, the malignant growth was limited to the endometrium without gross or histologic evidence of myometrial

TABLE III.—INCIDENCE OF MYOMETRIAL INVASION IN 62 CASES

	No. of cases
Untreated group	31
Irradiated group	6
Total	37*

*60 per cent of 62 specimens.

TABLE IV.—SURGICAL-PATHOLOGIC CLASSIFICATION OF 62 CASES OF ENDOMETRIAL CANCER, DISTRIBUTION OF CASES

	1946 to 1952		*1953 to 1956*	
Pathology	*Untreated*	*Irradiated*	*Untreated*	*Irradiated*
Stage 0	13	3	8	1
Stage I	12	2	13	2
Stage II	1	1	1	1
Stage III	1	0	3	0
Stage IV	0	0	0	0
Total	27	6	25	4

invasion in 40 per cent of the cases, as shown in Table II. There was myometrial invasion in 37 specimens or 60 per cent of the total as shown in Table III. Myometrial invasion was present in 31 of the untreated group of 52 cases, an incidence of 60 per cent, while 6 of the 10 irradiated myometria revealed viable tumor.

CLASSIFICATION

Because of its inaccessible location, macroscopic diagnosis of endometrial cancer is often difficult. A surgical pathologic classification suggested by Javert (7) in 1952 combines the stage of the disease at operation with the histologic findings in the surgically removed specimen. He placed lesions limited to the endometrium in stage 0, lesions limited to the uterus in stage I, adnexal spread in stage II, lymph node metastases in stage III, and carcinomatosis in stage IV. Table IV indicates the distribution of cases in this series according to this classification.

TABLE V.—POSTOPERATIVE COMPLICATIONS, CORRECTIVE TREATMENT

	Cases		*Surgical*	*Conservative*	*Improved*
	No.	*Per cent*			
Early					
Urinary fistulas	5	8.1	3	2	5
Ureterovaginal (4)					
Vesicovaginal (1)					
Vascular	7	11.3	0	7	7
Pelvic hematoma (2)					
Thrombophlebitis lower extremity (5)					
Inflammatory	1	1.6	–	1	1
Pelvic abscess (1)					
	13	21	3	10	13
Late					
Urinary	3	4.8	1	2	3
Stress incontinence (1)					
Pyelonephritis (2)					
Others	1	1.6	1	—	1
Small bowel obstruction (1)					
Total	17	27.4	5	12	17

Does not include 10 cases of mild bladder atony.

PREOPERATIVE CARE AND OPERATION

Adequate preoperative preparation is most important. If anemia is present it is corrected by whole blood transfusions, preferably 48 hours before surgery. Nutritional deficiencies are improved by a high protein, high vitamin diet. Associated medical conditions are treated accordingly with particular attention paid to existing or latent diabetes, hypertension, and vascular disease. In addition to routine bowel preparation with laxatives and enemas, on the day before operation, a Miller-Abbott tube is passed into the small intestine by using fluoroscopy if necessary. In our experience the Miller-Abbott tube has been extremely useful and serves two important purposes: (1) it provides decompression of the small bowel thus allowing for excellent operative exposure; and (2) it is useful in combating postoperative paralytic ileus, which frequently follows trauma incident to the extensive resection.

TECHNIQUE OF THE OPERATION

The technical aspects of the operation have been described in detail by Meigs (10) and more recently by Parsons and Ulfelder, hence only its essential features will be reviewed at this time. A preliminary curettage is a routine part of the procedure. The patient is then placed in the supine position and the peritoneal cavity is entered through a left paramedian muscle-retracting incision in the lower part of the abdomen. The ureters are mobilized through their entire course from the sacroiliac level to the bladder with particular care so as not to strip them free of their peritoneal covering and thus

jeopardize their blood supply. The bladder is mobilized and the uterine arteries are divided and ligated at their origin. The obliterated hypogastric and superior vesicle arteries are dissected free and gently retracted upward with the bladder. The lateral pelvic web is then divided and ligated on either side. This step is followed by complete en bloc removal of the uterus, both tubes and ovaries, and all the lymphatics and lymph node-bearing tissue between the two pelvic walls, including a 5 centimeter cuff of vagina and peritoneum of cul-de-sac (Fig. 1). Bilateral excision of the common, external and internal iliac, obturator, and parasacral lymph nodes completes the dissection. A rubber drain through the vagina reduces the incidence of pelvic hematoma and complicating sepsis. Adequate postoperative care entails particular attention to the electrolyte and fluid balance and prevention of complications.

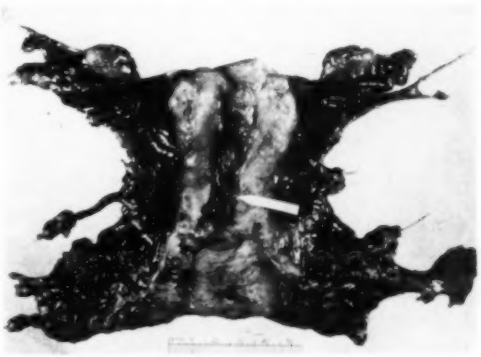


FIG. 1. Wertheim specimen. Note wide segments of resected parametrial and paravaginal tissue.

MORBIDITY

Nonfatal postoperative complications are outlined in Table V. Those which altered the immediate postoperative course were termed early, and those sequelae that were manifested during the late convalescent period were referred to as late. The 13 early complications included 5 urinary fistulas or 8 per cent of the patients operated upon. One patient who required a nephrostomy died with recurrent carcinoma 11 months later. This patient had had previous irradiation therapy. One patient in whom bilateral ureterovaginal fistulas developed had improved following bilateral ureterovesical anastomoses but died 5 months later from unknown cause. One vesicovaginal fistula was successfully repaired. This patient had received preoperative x-ray therapy. The other 2 ureterovaginal fistulas healed spontaneously.

This study, as well as others, points to urologic complications as constituting a major challenge following the Wertheim procedure. Brunschwig (2) reports 6 urinary fistulas or an incidence of 11 per cent in 57 patients with carcinoma of the endometrium undergoing Wertheim hysterectomy. Liu and Meigs noted 45 fistulas of all types in their 473 Wertheim hysterectomies performed for both cancer of the cervix and endometrium, an incidence of 9 per cent.

Second only to the fistulas, bladder atony and incontinence are the most annoying sequelae. While most patients experience some loss of bladder sensation for several weeks, a few still continue to have bladder atony for several years. Ten patients in this series complained of a loss of bladder sensation with variable degrees of incontinence. Symptoms lasted from 6 months to 2 years in most cases. One patient improved very slowly over a period of 4 years. In 1 case stress incontinence was severe enough to require a Marshall-Marchetti repair. Only 2 of the 4 patients with late urinary sequelae had received preoperative irradiation. Upper urinary tract infection occurred in 2 patients who had received previous irradiation. In both instances marked radiation fibrosis had caused ureteral stricture and hydronephrosis. One patient was readmitted 6 months later and was successfully operated upon for a small bowel obstruction due to adhesions. Of the 7 vascular complications none required surgical intervention. In 1 patient pelvic sepsis developed which responded satisfactorily to drainage and antibiotics.

TABLE VI.—ANALYSIS OF EARLY AND LATE DEATHS

Patient Age, years	*Stage disease*	*Operation*	*Node involvement*	*Length survival*	*Outcome and autopsy findings*
L. G. 60	III	W-n	Positive	(O.D.) 26 days	Autopsy: Pos. aortic nodes, septic emboli. Cirrhosis liver
F. B. 65	I	W-n	Negative	1 month	Discharged to mental hospital. Autopsy not done
M. H. 65	0	W	—	3 months	Died pneumonia at home N.E.R.
M. M. 64	0	W-n	Negative	5 months	Died at home, cause undetermined. N.E.R.
B.T. 71	I PR	W-n	Negative	8 months	Autopsy: recurrence vagina, abd. wall and retroperitoneum
M. Mc. 59	I PR	W-n	Negative	11 months	Autopsy not done
E. B. 65	I	W-n	Negative	2 years	Autopsy not done. N.E.R.
J. L. 45	III	W-n	Positive	3 years	Autopsy not done. Clinical recurrence in pelvis
L. D. 52	0 PR	W-n	Negative	5.5 years	Autopsy not done. N.E.R.
E. D. 75	I	W	—	7 years	Autopsy not done. N.E.R.

W: Wertheim hysterectomy.
W-n: Wertheim with bilateral pelvic node dissection.
PR: Previous radiation.
O.D.: Operative death.
N.E.R.: No evidence of recurrence.

MORTALITY

There was 1 hospital death, giving an operative mortality of 1.6 per cent. This 60 year old patient with extensive disease involving myometrium and pelvic nodes died 26 days after surgery as a result of ileus and pelvic sepsis. Autopsy revealed positive para-aortic nodes, multiple septic emboli, and cirrhosis of the liver. Of the 9 late deaths, 3 were from cancer while 5 were of intercurrent disease (Table VI). Two patients survived more than 5 years with no evidence of recurrence. In 1, recurrence developed 3 years postoperatively and she died thereof. This patient had had positive nodes. Of the 3 patients who had received preoperative irradiation, 2 died from carcinoma within 1 year of surgery. One patient with severe radiation reaction associated with stricture of the sigmoid required a transverse colostomy. The third patient died of intercurrent disease 5.5 years postoperatively without evidence of recurrence. One death occurred in a 65 year old patient who was transferred to a mental hospital on the tenth postoperative day with a diagnosis of psychosis. She died 1 month later from pyelonephritis. No autopsy was performed.

TABLE VII.—THREE AND 5 YEAR END RESULTS

	3 year salvage			*5 year salvage*		
	No. of patients	*Alive*	*Per cent*	*No. of patients*	*Alive*	*Per cent*
Untreated primary group	41	37	90	27	22	81.5
Without myometrial invasion	18	16	88	13	12	92.
With myometrial invasion	23	21	91	14	10	71.
With positive lymph nodes	4 patients: 1 operative death, 1 lived 3 years, and 2 are alive and well 2 years					
Untreated primary and irradiated group	51	44	86	33	26	78.8

END RESULTS

Thirty-three of the 62 patients subjected to the Wertheim hysterectomy are now suitable candidates for 5 year study. Twenty-six of the 33 patients survived 5 years or more without recurrence, an absolute 5 year cure rate of 78 per cent. Two patients are now

TABLE VIII.—VAGINAL RECURRENCES

Patient	*Surgical pathology*	*Site*	*Time*	*Treatment*	*Outcome*
B. I.	Adenoca. stage I (P.R.)	Vagina	8 mos.	None	Died
R. B.	Adenoacanthoma stage I	Vagina	11 mos.	Vaginectomy	Alive and well 6 yrs.
J. L.	Adenoacanthoma stage III (P.N.)	Pelvic wall	3 yrs.	None	Died

P.R.—Previously irradiated. P.N.—Positive nodes.

alive and well 10 years after surgery. In Table VII the 3 and 5 year end results are summarized.

The 5 year survival rate for the previously untreated group (22 out of 27) was 81 per cent. When the lesion was confined to the endometrium the 5 year salvage was 92 per cent, but when myometrium was involved the figure dropped to a low 71 per cent. Of the 4 patients with positive lymph nodes, 2 are alive 2 years and 1 lived 3 years and died postoperatively of advanced disease.

RECURRENCE

There were 3 pelvic recurrences or an incidence of 5 per cent. In Table VIII these recurrences are outlined in terms of pathology, time, site, and end results. Two of these recurrences occurred within the first year, the other 3 years postoperatively. This latter case is of special interest, having shown both myometrial and lymph node involvement. Two of these patients ultimately died of their disease, while the third is still living and well 6 years following vaginectomy.

In general, the more advanced the lesion the earlier is the appearance of recurrence. Finn noted that in those patients with recurrence who had shown histologic evidence of deep myometrial invasion, the average postoperative time interval was 1.7 years. He also states that the most common sites of recurrence were vagina, bladder, and the remaining pelvic peritoneum and lymph nodes. Meigs (11) in a study of 25 recurrences found 24 of them confined to the vagina, 11 of these on the anterior vaginal wall. Of 14 vaginal metastases reported by Way, 13 occurred beneath the urethra, 1 centimeter from the introitus.

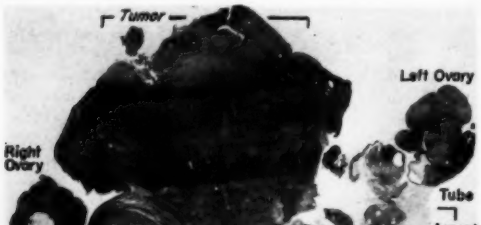
These frequent findings, we believe, are strongly suggestive of a constant pattern of lymphatic spread, a type of extension that occurs by tumor emboli rather than by direct permeation.

DISCUSSION

It is generally agreed that cancer of the uterine body has not been studied nearly as critically as cancer of the uterine cervix. From available data it has been shown that, in cancer of the endometrium, cure rate of 85 per cent can be reached when the lesion is diagnosed and treated early. In this regard when the growth is strictly limited to the endometrium, the usefulness of surgery and irradiation is similar. The chances of cure are equal with either form of therapy. If we consider patients as they first arrive, often with advanced disease, the cure rate is about 50 per cent by all types of treatment. This group represents patients whose disease in many instances has progressed through the myometrium and has encroached on adjacent structures. It is this group which poses the most critical problem.

Once endometrial cancer breaks through the myometrium, its growth is accelerated and histologically will reveal varying degrees of malignancy. The rapidity of spread to the regional lymph nodes is of extreme importance to the surgeon. Further observations, however, are needed before it can be decided whether or not the lymph nodes are involved early in the course of the disease. It is often stated that nodal metastases are in the majority of cases a terminal phase. This would suggest that such lymphatic involvement is part of a widespread extension. If, on the other hand, metastases to lymph nodes remain localized in the pelvis for a relatively long time, then radical extirpation would seem justified.

It is generally known that lymph nodes are involved in a much greater percentage of cases than was formerly believed. Javert



a

b

FIG. 2. F. M., aged 56 years, living and well 2 years postoperatively. Wertheim hysterectomy specimen. The entire uterus, tubes, ovaries, and parametrium were imbedded in toto and cut vertically into 120 serial sections at from 25 to 30 microns in thickness. a, This photograph shows level No. 50 with tumor present in left parametrial lymph node. b, Adenocarcinoma grade II in parametrial lymph node.

quotes 14 in 50 cases or 28 per cent. Liu and Meigs found regional lymph node involvement in 23 per cent of their 47 cases; others have reported similar incidence.

Myometrial invasion appears to be an intermediate stage in the natural progress of this malignant growth and its lethal potential should not be underestimated. Of the 36 patients with myometrial invasion in this series, 11 per cent had regional lymph node involvement. The correlation between myometrial invasion and incidence of positive nodes was even more clearly noted in the study of Liu and Meigs in which 10 of 22 cases with myometrial invasion had nodal involvement, while only 1 out of 25 patients with tumor limited to the endometrium had positive nodes.

A definite correlation between myometrial invasion and mortality has been shown in our 5 year survivals. Of the previously untreated group without myometrial invasion, 92 per cent lived 5 years while only 71 per cent survived 5 years when myometrium was already involved.

Carcinoma originating in the lower uterine segment and fundal lesions extending into the endocervical canal create a special problem. Since the lymphatic drainage from this region passes through paracervical channels in the same manner as does that of epidermoid carcinoma of the cervix, a Wertheim procedure with pelvic lymphadenectomy is imperative. Attempts to assess the extent of endometrial involvement by fractional curettage in our experience have not been very successful.

In every Wertheim procedure, it is our practice to have an assistant open the uterus upon removal while in the operating room. If the lower uterine segment is involved or there is any gross evidence of myometrial invasion, complete pelvic lymph node dissection is immediately carried out. Unfortunately, it is not always possible to detect these changes with the naked eye, in which cases frozen sections have been resorted to with some success. Not infrequently, however, all these measures may be of little assistance, and one then must pur-

sue the most judicious but uncompromising course.

Failures in the cure of endometrial cancer are usually the result of unsuspected clinical extensions. There may be unsuspected extrauterine spread, not only to tubes and ovaries, but also to pelvic nodes which cannot be detected by preoperative digital examination or by inspection at the operating table. It is doubtful if any form of conservative treatment short of radical excision could do much under these circumstances. The second source of failure is recurrence or residual carcinoma within the parametrial, paracervical, and paravaginal lymphatics following conventional treatment.

It is apparent that a better understanding of the lymphatic spread with relation to frequency, site, stage of the disease, and end results is of paramount importance. In an attempt to find objective evidence in this regard, recently we have begun a new program of histologic study, using giant microscopic sections of the entire Wertheim specimens. Figure 2 shows such a section with tumor present in parametrial lymph nodes but with no obvious direct spread from the primary lesion. This observation might suggest that endometrial carcinoma spreads to regional nodes by embolization with greater frequency than previously suspected and perhaps even in the presence of more differentiated lesions. Although no definite conclusions can be drawn at this time we hope that further observations will shed some light on this important question.

Finally, mention must be made of the discouragingly high rate of urinary tract complications. This problem, which has been difficult to solve, has precluded routine use of adequate radical surgery in the elderly, poor risk patients with endometrial carcinoma. Preventive measures designed to reduce fistulas, including omental grafts to the ureters and the use of ureteral catheters have met with only partial success. Avoiding complete mobilization and stripping of the ureters and a meticulous dissection of the bladder around the ureterovesical junction and the bladder base may ultimately prevent these most unfortunate sequelae. Novak, reporting on 100 cases of Wertheim hysterectomy with only 1 ureteral fistula, proposed that the ureters be transposed into the peritoneal cavity. This procedure, he believes, prevents extreme lateral fixation of the ureters and avoids angulation of their distal segment. This is our present method of dealing with the ureter. The prevention of postoperative pelvic sepsis should reduce the incidence of focal necrosis and ureteral perforations.

In addition to surgical alteration, there is a less tangible etiologic factor which may be responsible for the formation of some of these fistulas. This factor may be associated with an anomalous blood supply to the ureters. Daniel and Shackman, in their investigation of the vascular supply of 100 ureters, noted that 2 of these failed to receive branches from the renal and from the vesical or uterine arteries, while 10 had no vessels except for minute peritoneal twigs. They also observed that the anastomoses between the long ascending and descending vessels running in the periureteral connective tissue were deficient in from 10 to 15 per cent of the ureters.

SUMMARY AND CONCLUSION

A clinical analysis of 62 cases of endometrial carcinoma treated by the Wertheim hysterectomy has been presented. Bilateral pelvic lymph node dissection was carried out in 50 of these 62 cases while in the remaining 12 no pelvic lymph node dissection was done.

There were 52 adenocarcinomas, 9 adenoacanthomas, and 1 carcinosarcoma. Fifty-two were primary cases while in 10 previous irradiation had been received. Myometrial invasion was present in 37 cases or 60 per cent of the total group.

Among the 50 patients who underwent node dissection, 4 had lymph node involvement, an incidence of 8 per cent. Of the 37 patients with myometrial invasion 4, or 11 per cent, had positive nodes. Of these 4, 1

died in the hospital, 1 lived 3 years, and 2 are alive and well at 2 years. Complications occurred in 27 per cent of the cases; urinary tract disturbances accounting for 12 per cent of these. Urinary fistulas developed in 5 patients, an incidence of 8 per cent. Etiologic factors as well as practical preventive measures are discussed. Operative mortality was 1.6 per cent.

A brief description of the Wertheim procedure is given.

Pelvic recurrences in 3 patients are discussed in terms of pathology, site, time, and outcome.

The 5 year survival for the primary group was 81 per cent. The 3 year survival for this group was 90 per cent. When myometrial invasion was present the 5 year salvage dropped to 71 per cent.

The end results in this study compare favorably with those reported in the current literature and justify further evaluation of the radical surgical approach for the treatment of endometrial cancer. The high incidence of postoperative complications, however, impose heavy obligations on those who treat and care for these patients. It is our hope that future experience and observations will add to our knowledge of the metastatic spread of endometrial cancer, improve selection of patients, and reduce morbidity, at which time the Wertheim hysterectomy with pelvic lymph node dissection may prove worthy of more routine use.

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THE INFLUENCE OF EXPERIMENTAL ARTERIOVENOUS FISTULA ON THE HEALING OF FRACTURES AND ON THE BLOOD FLOW DISTAL TO THE FISTULA

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MUCH HAS BEEN SAID about the blood supply of bone and its implications in the healing of fractures. Even so, the role of the blood supply in the growth and healing of bone is not fully understood. It is obvious that for any tissue, including bone, to grow and make repair the arterial blood supply must be adequate. Furthermore, when a tissue is deprived of its arterial supply, it soon dies. The venous blood, on the other hand, is seldom given any credit for its constructive or reconstructive influence. Yet, evidence given by Bier and Blair indicates that the venous blood itself may have some regulatory or stimulatory effect on the healing of tissue.

HISTORICAL

Through several centuries many clinicians have been making observations on the effects of venous stasis in delayed union and healing of fractures. Ambroise Paré, in the sixteenth century, had in mind the therapeutic value of venous stasis when he said, "If, however, the callus is too small and undeveloped in consequence of the bandage being too tight or because the limb has been too long at rest without exercise or the nutrition of the patient was insufficient, the bandage has to be taken off and entirely removed from the fracture. Instead a different bandage should be applied beginning at the root of the vessels, if on the leg close to the inguinal region, if on the arm near the shoulder and reaching nearly to the site of the fracture. For by this remedy the blood is squeezed out and compelled to flow to the injured place."

Nicoladoni, Bruns, Thomas, and others in the nineteenth century, as mentioned by Bier, made observations on the beneficial results of venous stasis in nonunion or delayed union of bones. In Bier's text he described the therapeutic effects of passive hyperemia in the healing of fractures.

In the current century, Pearse and Morton (16–18) and McMaster and Roome have shown experimentally that venous stasis produced by venous ligation accelerated bone healing. Blair, Starr, Hutchison and Burdeaux, and others have described the histologic changes that venous stasis can produce in the periosteum, epiphyseal region, and bone.

Janes (10–11), with Musgrove and Elkins has used effectively the stimulus of an induced arteriovenous fistula to increase leg length, experimentally and clinically. There are many clinical examples of overgrowth of an extremity from infection, vascular anomalies, fracture, or other alterations which introduce the element of venous stasis.

PURPOSE, MATERIAL, AND METHOD

The induction of an arteriovenous fistula seemed an ideal procedure to obtain persistent venous stasis for a study on the rate of fracture healing. Also, since there is confusion in the literature as to the circulation distal to the fistula, the opportunity to study

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FIG. 1. Animal No. 4, 72 days after resection. Note the absence of bone regeneration on either side, the side with the fistula being at right of picture.

the distal circulation in the presence of such fistulas had value.

Therefore, this experimental study was designed to deal with two questions: (1) the influence of an experimentally produced arteriovenous fistula on the rate of fracture healing, and (2) the influence of the arteriovenous fistula on the circulation in the extremity distal to the fistula.

Four groups of adult mongrel dogs were used in the study, and the left external iliac vessels were the site of the arteriovenous fistulas established in all. Group 1 consisted of 4 animals, the controls, in which only the fistula was induced. Group 2 consisted of 9 animals in which 1 centimeter of the fibula

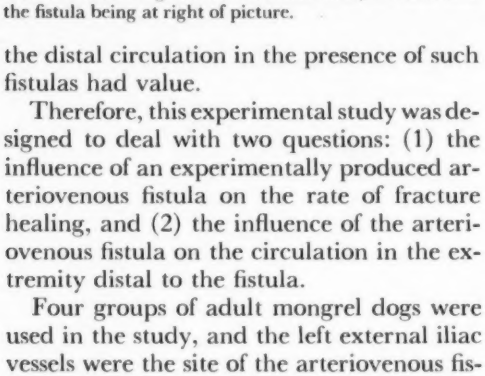

FIG. 2. From animal No. 19, 5 weeks after fracturing. No difference in the rate of union can be seen, the side with the fistula being at left of picture.

was excised subperiosteally from each leg and the fistula was established at the same operative period. Group 3 consisted of 8 animals in which the bilateral midfemoral shafts were fractured and fixed with four-hole plates and screws, and the fistula was established 1 week later. Group 4 consisted of 4 animals in which the left femur was fractured and the fistula was established during the same operative period.

Signs of union of the fractures induced were sought by periodic roentgenologic study; and as soon as evidence of union was present on either right or left, the animal was sacrificed and the fracture sites were studied microscopically. The fibulas from which a portion had been resected were similarly examined roentgenologically, but the animals were sacrificed at arbitrary intervals varying from 21 to 105 days after operation.

RESULTS

Group 1. In the 4 control animals, the unilateral arteriovenous fistulas in the left external iliac vessels remained patent during the observation periods and were patent when the animals were sacrificed.

Group 2. In the 9 animals in which a portion of each fibula had been resected, with immediate establishment of the fistula, no formation of bone to bridge the defect was found in any instance. A typical roentgenogram from this group (Fig. 1), taken 72 days after the operation, shows no regeneration of bone. At necropsy, a heavy fibrous cord was found connecting the ends of the fibula, but microscopically it consisted of dense connective tissue having no osteoid element.

Groups 3 and 4. These groups will be considered together, as they afforded no appreciable difference in the rate of fracture healing. These animals were sacrificed as soon as the roentgenograms showed early union on either side, a time which varied from 25 to 68 days after operation. In 7 of the 12 animals, union was complete bilaterally as revealed by roentgenologic, clinical, and histologic examination. In 3 other animals, the right femur had united and in 1 the left had

united. In the twelfth animal, union was not complete histologically in either leg, although roentgenologically it had appeared so.

A typical roentgenogram from one of these groups shows a well developed bridging and anchoring callus (Fig. 2); and under low power magnification the histologic sections from the fracture sites in the same animal at the seventh week exemplify the observation that when union was present bilaterally, no histologic difference could be detected in the rate of healing or the detail of the uniting fracture (Fig. 3).

In 1 animal (No. 18, group 3), the fistula spontaneously closed about the fourth week after it was formed; at necropsy the arterial side of the fistula was occluded, but the venous side remained patent.

Clinically, minimal edema developed during the postoperative period in the leg with the fistula. The fixation of the fracture was an important influencing condition, however; if motion occurs at the site of fracture, the extent of the edema becomes considerable according to Johnson. Also on the side with the fistula, a venous pattern was increasingly prominent with the formation of varices similar to those reported by Deterling and others. This vascular dilatation and tortuosity was most marked in a region extending over the lateral aspect of the thigh and the lower abdomen.

Increased venous pressure near the fistula, noted by Holman, was observed in this study also when blood was being drawn from the left femoral vein. The blood was under pressure, had a pulsatile flow, and was darker than blood from the normal side. These findings suggest venous stasis on the side with the fistula, as well as an increased venous pressure. After establishment of the fistula there was progressive fibrosis about the neurovascular bundle and the diameter of the femoral artery was diminished from the normal.

Polyvinyl acetate casts of the fistulas in 21 of the 25 animals were made. These were used to measure the circumference of the fistulas directly by tying a small silk thread about each and then measuring its length. Examples of the casts are shown in Figure 4.

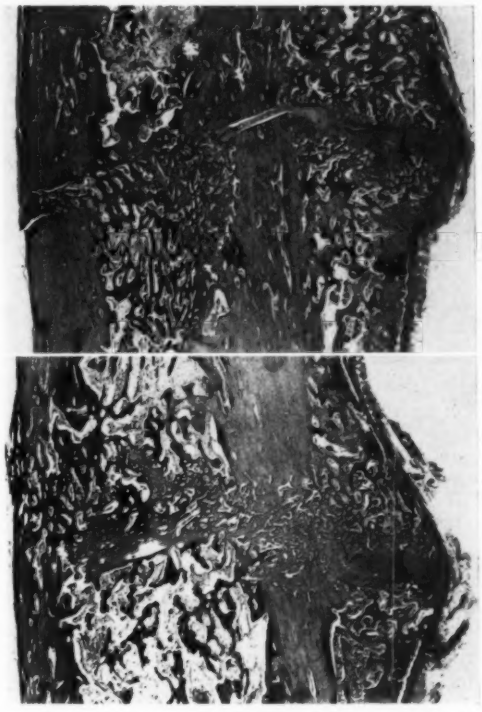

FIG. 3. Low power magnification of fracture sites (left, *above;* right, *below*), showing no histologic difference in the union. Hematoxylin and eosin, ×5.

The fistulas varied in circumference from 2.1 to 5.2 centimeters. In 10 of the animals, competent venous valves were found distal to the fistulas when the casts were made. The size of the fistulas had no correlation with the other findings to be reported (Tables I, II, and III).

OBSERVATION ON THE CIRCULATION DISTAL TO THE FISTULA

To gain better understanding of the circulation distal to the fistula, several measurements were made for comparison of the leg with the arteriovenous fistula (left) with the contralateral control leg (right). The temperature of various locations on the hind legs was recorded in all of the animals. The rate of blood flow in the femoral artery was meas-

TABLE I.—TEMPERATURE DIFFERENTIAL (DEGREES C.) FROM CONTROL LEG TO COUNTERPART DISTAL TO ARTERIOVENOUS FISTULA

Animal No.	*Circumference of fistula, cm.*	*Muscle of thigh*		*Subcutaneous area of:*		
				Thigh		*Ankle*
		Inside	*Outside*	*Inside*	*Outside*	
2	3.5	0.5	1.9	1.1	1.9	
4	5.0	0.3	0.1	0.3	1.0	−1.4
5	3.8	−0.1	0.4	−0.2	0.2	
6	3.3	1.0	0.4	0.4	0.4	
7	2.8	0.6	0.9	0.7	0.9	
9	2.4	0.6	0.5	1.2	1.2	
11	5.2	0.4	0.2	0.0	−0.1	−0.5
12	4.2	0.4	0.2	0.2	1.4	
13	4.6	0.3	0.2	−0.4	0.8	−0.4
14	3.4	0.5	0.1	0.2	0.6	−3.3
15	2.6	0.6	0.3	−0.1	0.3	−0.9
16	3.3	0.3	0.1	0.3	0.4	−1.3
17	2.2	0.9	0.9	0.2	0.6	−2.0
18*	—	0.7	0.6	−0.3	1.5	1.1
19	2.3	0.6	1.2	−0.2	0.8	−0.5
20	3.1	0.7	0.9	0.6	2.0	−4.1
21	4.3	0.7	0.1	−0.2	1.2	−1.7
22	2.6	0.5	0.4	0.2	0.5	−1.4
24	2.3	0.7	0.3	−0.3	1.5	−1.5
Average differentials†		0.57	0.54	0.21	0.95	−1.49

*Fistula closed spontaneously about fourth week.
†Animal No. 18 excluded.

ured in 11, and the oxygen content and saturation of the venous blood were determined in 7. By utilization of radioactive iodinated human serum albumin (RIHSA), the blood flow and equilibration curves in the hind legs were plotted for 5 animals.

Studies of temperature. Recordings of temperature were made from the muscles and subcutaneous areas of the thighs of all the animals, and from the subcutaneous area of the ankles of 13. The recording equipment consisted of needle thermocouples connected to a calibrated rheostat and deflecting galvanometer.

TABLE II.—EFFECTS OF ARTERIOVENOUS FISTULA IN LEFT EXTERNAL ILIAC VESSELS ON BLOOD FLOW IN LEFT FEMORAL ARTERY

Animal No.	*Circumference of fistula, cm.*	*Femoral-artery flow, c.c. per min.*		*Per cent of flow in counterpart*
		Right	*Left*	
4	5.0	544	188	35
5	3.8	498	264	53
11	5.2	432	140	32
12	4.2	408	168	41
14	3.4	520	136	26
16	3.3	416	200	48
18*	—	244	168	69
19	2.3	464	160	35
21	4.3	380	104	27
22	2.6	628	240	38
24	2.3	368	144	39
Average†				44

*Fistula closed.
†Animal No. 18 excluded.

The differences in temperature between the side with the fistula and the control side are given in Table I. Records from 6 of the 25 animals were excluded because of technical difficulty at the time of the recording. The tabulation shows a generally elevated temperature of the thigh on the side with the fistula. In the muscles the increase averaged 0.62 degree C. on the inside of the thigh and 0.5 degree C. on the outside. In the subcutaneous area, however, the temperature of the inner aspect of the thigh was increased by an average of only 0.1 degree C., and the outer aspect of the thigh by 0.94 degree C. This is not surprising when one considers the greater vascularity of the outer aspect of the thigh.

In the ankle, the temperature on the side with the fistula was consistently low, averaging 1.58 degrees C. lower than the control side. As Brooks and Johnson have pointed out, this decrease is directly related to the blood flow.

In animal No. 18, in which the fistula had closed, the temperature of the ipsilateral ankle was 1.1 degrees C. higher than that on the control side. This same change occurs if a quadruple ligation of the fistula is applied.

Blood flow in the femoral artery. In 11 animals the quantity of blood obtained from the femoral artery distal to the fistula was measured. This was done by inserting a catheter in the femoral artery at the mid-thigh and measuring the quantity of blood that flowed into a graduated cylinder in a specified time.

As can be seen from Table II, the average blood flow in the femoral artery on the side with the fistula was reduced to approximately 40 per cent of that in the control leg. This general decrease is due to the shunting of blood away from the artery by the fistula and to the reduced size of the femoral artery on the side with the fistula. The flow in the animal in which the fistula had closed spontaneously was greater than in those with a patent fistula, being reduced only to 69 per cent of normal. This points to the fact that in the presence of an arteriovenous fistula the collateral circulation is inefficient. Probably the condition results from the altered hemodynamics distal to the fistula—the increased venous pressure and venous stasis. When the fistula is closed or excised, the collateral circulation is more efficient, but does not establish a normal distal flow.

Oxygen studies of the femoral blood. Samples of venous blood were drawn from the femoral veins at the midthighs of 7 animals. These samples were analyzed for their oxygen content and capacity, and from these quantities the percentage saturation of the blood was calculated (Table III).

The oxygen content of the femoral venous blood was lower by an average of 1.24 cubic centimeters per 100 cubic centimeters on the side with the fistula. This amounted to an average decrease of 8 per cent in the saturation, which was due to the venous stasis present as a result of the arteriovenous fistula. The findings indicate that retrograde flow did not occur in the veins distal to the fistula, and that the venous blood distal to the fistula was not arterialized.

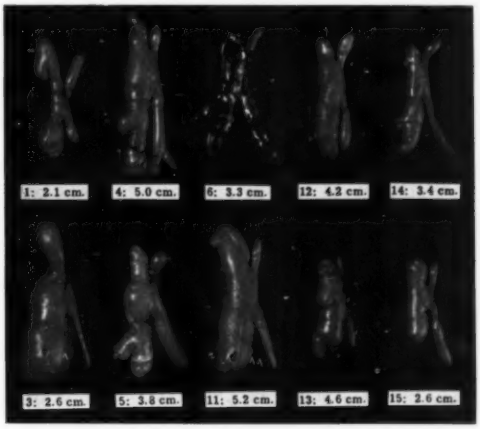

FIG. 4. Polyvinyl acetate casts of arteriovenous fistulas, with distal limbs downward. The circumference is reported below each cast.

Studies with RIHSA. With intravenous injection of RIHSA, the circulation in the hind legs of 5 animals was evaluated. This technique, used by Krieger and by Halligan and co-workers to evaluate peripheral circulation in humans, is easily adapted to the dog. With collimated scintillation counters placed over each malleolus and the counters connected to count-rate meters, 80 microcuries of RIHSA were injected into a foreleg

TABLE III.—OXYGEN IN BLOOD OF FEMORAL VEINS WITH ARTERIOVENOUS FISTULA OF LEFT EXTERNAL ILIAC VESSELS

Animal No.	Circumference of fistula, cm.	Content, c.c. per 100 c.c.		Capacity, c.c. per 100 c.c.		Saturation, per cent		Difference in per cent saturation
		Right	Left	Right	Left	Right	Left	
4	5.0	8.4	6.8	13.1	13.2	63.4	50.8	13
11	5.2	15.6	14.6	17.5	17.2	88.0	83.7	4
16	3.3	12.3	11.6	14.1	15.2	85.8	75.0	11
17	2.2	6.4	4.8	16.1	16.1	39.1	29.2	10
19	2.3	13.3	12.7	15.4	15.2	85.1	82.2	3
21	4.3	8.8	6.2	18.4	18.4	47.3	33.2	14
22	2.6	13.3	12.7	15.4	15.2	85.1	82.2	3

Averages: right-to-left difference in content, −1.24 c.c. oxygen per 100 c.c. blood; right-to-left difference in per cent saturation, −8 per cent.

TABLE IV.—RIHSA STUDIES IN ARTERIOVENOUS FISTULA OF LEFT EXTERNAL ILIAC VESSELS

Animal No.	*Time lag equilibrium, sec.*	*Equilibrium counts per sec.*					
		Abdomen		*Knee*		*Ankle*	
		Right	*Left*	*Right*	*Left*	*Right*	*Left*
3	Ankle 80	184	237	74	79	28	27
16	Ankle 60	338	406	145	194	44	51
18*	Ankle 0	487	457	276	356	161	212
21	Ankle 160	193	252	89	95	31	31
24	Ankle 100	142	163	41	63	13	14
	Knee 80						
Average lag †	96						

*Fistula closed.
†Animal No. 18 excluded.

vein. Continuous recordings were made until the activity in the ankles reached its level of equilibrium—approximately 2 to 4 minutes on the slower side. The curves then were normalized to eliminate the effects of differences in animal size and blood volume. The ordinate of the completed curve thus represented the moment-to-moment percentage attainment of the ultimate equilibrial count rate, and the abscissa represented time. After injection the maximal deviation of experimental data from the final smoothed curve was 2.5 units on the ordinate scale.

The equilibration curves for the 5 animals are shown in Figures 5 and 6. Six sets of curves are illustrated, since in 1 animal an equilibration curve was made for the knee as well as the ankle. The difference in the time at which the two curves of a set reach 100 per cent is due to the reduction of arterial supply and the venous stasis. Termed the "time lag," it is recorded below the curves and in Table IV.

Three general observations can be based on the curves from animals in which the fistula was patent. The curve from the side with the fistula (1) is delayed in starting, (2) varies from the control in respect to slope, and (3) reaches the 100 per cent level considerably later than the control (forms a time lag). It may be that the slope of the curve represents the arterial inflow and the changes in the venous compartment.

In the last set (animal No. 18, in which the fistula had closed) the curves actually were superimposed; and the tracing from the side with the fistula has been moved slightly to the right so it may be seen. This set represents the normal circulatory pattern, even though the total volume of blood was reduced.

The count rates measured at equilibrium when the counter was placed with the collimator at a fixed distance from the skin over the fistula, the medial side of the knee, and the medial side of the ankle, and over corresponding places on the control limb are given in Table IV. As equal volumes of blood in a given animal would have the same radioactivity, each reading indicates the volume of blood in the field of the scintillation counter. From the tabulation one can see that the highest counts were recorded over the patent fistulas and at the medial side of the ipsilateral knees. This is in keeping with the fact that the quantity of blood in these regions was greater as an effect of vascular changes shown by the arteriogram and RIHSA studies. Since the total volume of blood at the ankle is minimal, the difference in the count rates recorded there was small. This is in contrast with data from the animal in which the fistula had closed. In this animal the control side of the abdomen (opposite the site of the closed fistula) gave the highest counts. This could be expected, because the fistula no longer was pooling blood in the abnormally dilated pelvic veins. Since the impedance to collateral circulation had been removed by the closure of the fistula (as shown by the elevated temperature and increased blood flow), increased radioactivity at the knee and ankle could be expected also; and this too was found.

Aortograms. Percutaneous or direct abdominal aortograms were made in 9 animals. Our findings were similar to those reported by others. They demonstrated the heavy network of dilated, tortuous vessels in the region of the fistula, the majority of the vessels being venous. From the inguinal ligament to the knee, the arterial collateral vessels were visualized easily on the side with the fistula, where they appear dilated and tortuous. However, their counterparts on the control side were visible also, though less prominent. As others have found, this dilatation and tortuosity of the collateral arterial vessels just distal to the fistula are results of the venous stasis and venous pressure caused by the fistula. These collateral vessels in the thigh and their counterparts on the control side are illustrated in Figure 7.

In the animal in which the fistula closed, the collateral arterial vessels appeared somewhat tortuous, but certainly no more prominent than those on the control side; and the absence of the dilated and tortuous veins seen about the closed fistula was noteworthy (Fig. 8).

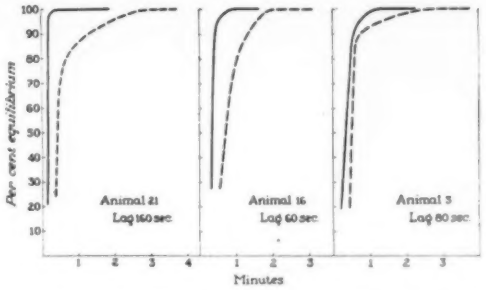

FIG. 5. RIHSA equilibration curves. The solid line represents the control side, and the broken line the side with the fistula.

COMMENT

Healing of fractures. Initially, we assumed that the arteriovenous fistula would produce a venous stasis which would be effective in accelerating union of the fracture. Sufficient evidence is presented in the literature to warrant the conclusion that venous stasis increases the rate of fracture healing. In the current experiment, the presence of venous stasis was shown by increased venous pressure, varicosities, and reduced oxygen saturation of the blood in the femoral veins. However, we could not demonstrate any change in the rate of fracture healing in the presence of the arteriovenous fistula.

Our application of arteriovenous fistula to induce venous stasis added one more variable to the problem in the demonstrated marked reduction of arterial supply to regions distal to the fistula, including the site of fracture. We can only surmise, then, that the reduction of arterial supply counterbalanced any stimulatory effects of the venous stasis. If the fistula had been at the level of the fracture, perhaps more positive results would have been obtained.

Circulation distal to the fistula. Our experimental work has demonstrated the hypothesis of Holman (6, 7) that since most of the blood delivered to the fistula is shunted into the venous tree, the amount of blood delivered below the fistula is reduced. This change was reflected in the time lag of the RIHSA studies and in the differential temperature studies, as well as in the reduction of approximately 60 per cent in measured blood flow. Pinotti and co-workers have shown that in dogs the pressure distal to the fistula is reduced by 75 to 100 millimeters of mercury, and that the reduced continuing flow is abnormal in its hemodynamics.

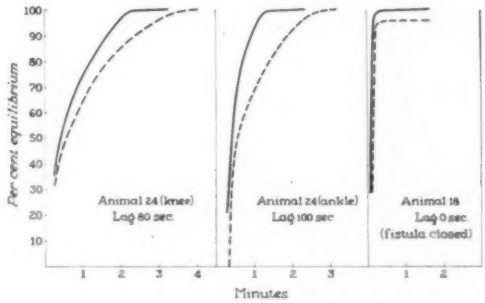

FIG. 6. RIHSA equilibration curves. The solid line represents the control side, and the broken line the side with the fistula.

FIG. 7. Aortogram from animal No. 24, the side with the fistula being at right in picture. Dilated tortuous vessels are visible about the pelvis.

Venous stasis in the limb, another result of the arteriovenous fistula, was reflected by increased venous pressure, varicosities, and reduced oxygen saturation of the venous blood distal to the fistula. This increased venous pressure and stasis also causes dilatation and tortuosity of the collateral arterial vessels immediately distal to the fistula, as seen by arteriography.

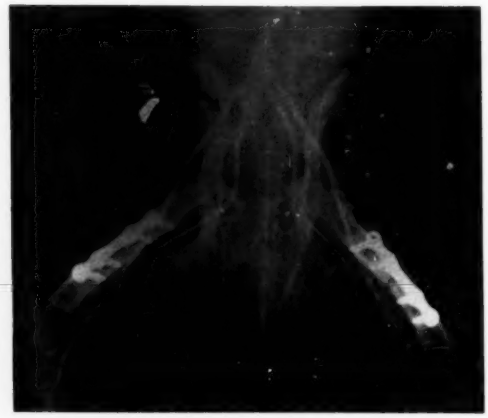

FIG. 8. Aortogram from animal No. 18, arrow pointing to interruption of artery at site where fistula closed spontaneously at about fourth week after induction.

SUMMARY

This experimental study was designed to determine the effects of an arteriovenous fistula on healing of bone and to investigate the circulation in the limb distal to the induced fistula. An arteriovenous fistula was established in the left external iliac vessels of 25 adult mongrel dogs, in conjunction with partial resection of each fibula, or with fractures of the left or bilateral femurs in 21 of them. The right legs served as controls.

The 9 animals subjected to partial resection of the fibulas were sacrificed at various intervals for study of regeneration of bone, but none was found.

The fractures in the other 12 animals were checked periodically by roentgenogram, and the animal was sacrificed as soon as healing became evident. Microscopically, roentgenologically, and clinically, no difference in the rate of fracture healing could be demonstrated between the limb with the normal circulation and the one with the arteriovenous fistula.

The circulation of the extremity was studied by recording of temperatures, measurement of arterial blood flow, determination of the oxygen content of the venous blood, and arteriography. Injection and monitoring of RIHSA revealed a significant time lag in attainment of equilibrium on the side with the fistula as compared with the control side. It was apparent from the data that the arterial blood supply was decreased in the limb distal to the arteriovenous fistula. Venous stasis was present distal to the fistula, and the oxygen content of the venous blood was reduced. Retrograde flow or arterialization of venous blood in the limb distal to the fistula was not demonstrated.

CONCLUSIONS

1. The presence of an arteriovenous fistula proximal to a fracture site does not speed the healing of the fracture.

2. The circulation distal to an arteriovenous fistula is greatly altered. This is due to the reduced arterial flow, the persistent venous stasis, and the inadequacy of the collateral arterial vessels.

3. Distal to the fistula there is no retrograde flow in the veins and the blood is not arterialized.

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COMBINED RADIOLOGIC-SURGICAL TREATMENT OF CARCINOMA OF THE CERVIX

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THERE IS NOT, nor should there be any attempt to make the surgical treatment rival radium and x-ray treatment. The two methods are partners in the attack on the disease, for unquestionably some patients will be cured by the one method and not by the other. —JOE V. MEIGS (3).

SINCE the pioneer work of Meigs on the surgical treatment of carcinoma of the uterine cervix was presented in 1944, a number of articles have been published on the subject. Today there can be no doubt that both the radiologic and the surgical treatment have a place in the therapy of carcinoma of the uterine cervix, although there is in practice a tendency to favor one or the other method.

By a treatment which combines both methods, it may be assumed that the patient is given a better chance of being cured, but relatively few articles dealing with this combined treatment are to be found in the literature. It is apparently thought that this treatment is more dangerous because more damage will be done to the ureters, bladder, and rectum.

This study was undertaken to investigate the anatomic spread of cancer of the uterine cervix in stage I patients, and to analyze the dangers to the ureters of the combined radiologic-surgical treatment.

THE MATERIAL

At the Norwegian Radium Hospital the policy is to give irradiation therapy to patients with carcinoma of the uterine cervix. Since 1937 the results have been published in the *Annual Report of Treatment in Carcinoma of the Uterus*. A combined radiologic-surgical treatment (prophylactic hysterectomy) has, however, been used in some few selected stage I and II patients, but since 1954 the radical hysterectomy with bilateral dissection of the pelvic lymph nodes has been given priority when the combined treatment is used.

Two hundred and sixty-six patients with the disease in stage I (not including patients with stage 0 lesions) were admitted to The Norwegian Radium Hospital in 1954, 1955, and 1956. For various reasons it was not possible to perform radical surgery on all these stage I patients, and only 96 of them underwent radical surgery and preoperative radium treatment. So the material is a selected one, and on the whole the patients were young and in relatively good condition (Figs. 1 and 2).

All the patients were admitted to the hospital as soon as possible following diagnosis, and here they underwent a thorough examination. The clinical staging of the disease was always made under nembutal anesthesia, and the examination of the renal tract always included examination of the urine, blood urea, cystoscopy, and urography. There were 88 cases of squamous cell carcinoma, 1 case of adenocarcinoma, and in 7 cases the diagnosis was undifferentiated carcinoma. Two patients were pregnant, in their third and fourth month respectively, and 1 patient had had a delivery 3 months before the diagnosis was made. Three patients were unmarried, and 2 of them had never been pregnant; the third had had 2 children.

THE COMBINED RADIOLOGIC-SURGICAL THERAPY

All the patients were primarily given radium to the tumor representing 6,000 to

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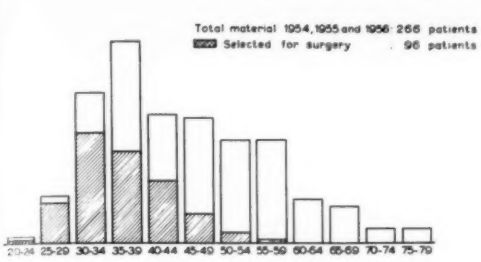

FIG. 1. Age distribution of patients with carcinoma of uterine cervix, stage I.

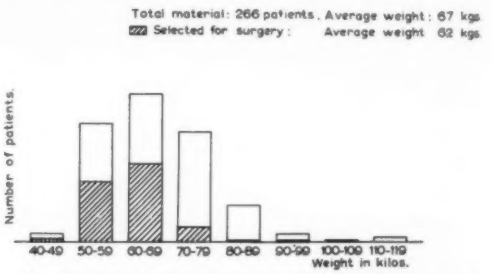
Total material: 266 patients. Average weight: 67 kgs.
Selected for surgery: Average weight 62 kgs.
Number of patients.
40-49 50-59 60-69 70-79 80-89 90-99 100-109 110-119
Weight in kilos.

FIG. 2. Weight distribution of patients with carcinoma of uterine cervix, stage I.

7,200 milligram hours in 1 or 2 fractions (30 milligrams of radium in vagina and 20 to 30 milligrams of radium in uterus for 5 days).

The patients selected for combined therapy, following the radium treatment, were discharged for 6 to 8 weeks and then readmitted to the hospital for radical hysterectomy and pelvic lymphadenectomy. The patients not selected for the combined treatment, immediately after the radium treatment, underwent a complete course of x-ray therapy including a 3,000 roentgen skin dose to each of 2 anterior and 2 posterior pelvic ports.

The operations have all been performed by the writer personally. As to the technique of the operation, the lymphadenectomy was always done before the hysterectomy. Stress was always laid on the complete removal of the paracervical and paravaginal fatty tissue of the pelvic floor and the pelvic wall, and also on the dissection and removal of the fatty tissues and the lymph nodes surrounding the pelvic vessels and nerves. The pelvic ureter was separated from its peritoneal and extraperitoneal surface, but the periureteral vascular plexus was not stripped from the ureter between the points where it crosses the common iliac vessels and where it enters into the bladder. As the last step in the operation the uterus with the parametria, tubes and ovaries, and the upper third or quarter of the vagina was extirpated and the vagina closed without any drain. On completion of the operation an indwelling catheter was placed in the bladder and left there for about 10 days. Ureteral catheters during operation were not used.

The operation was performed on 94 patients. In 2 cases the uterus with the tubes and ovaries, parametria, and the upper third of the vagina were extirpated, but numerous lymph nodes on both sides of the pelvic wall were so infiltrated with metastases, which partly invaded the external and internal iliac vessels, that a radical dissection seemed hopeless. Consequently, only 1 lymph node from each side was extirpated for microscopic diagnosis (squamous carcinoma in both cases).

PATHOLOGIC STUDY OF SURGICAL SPECIMENS

After being photographed (Fig. 3) the surgical specimens were in all cases immediately sent to the pathological laboratory of the hospital for examination, and the findings are shown in Table I.

As will be seen, in 16 cases a residual carcinoma was present in the cervix, and in 18 cases metastases were diagnosed in the regional lymph nodes. In 12 of these 18 cases there was no residual carcinoma in the cervix. The localization of the metastasized lymph nodes is shown in Figure 4. Unfortunately, serial sections were not done, and it is possible, therefore, that some metastasized lymph nodes may not have been diagnosed.

PRELIMINARY RESULTS

It is not within the scope of the present article to discuss the results of the therapy in

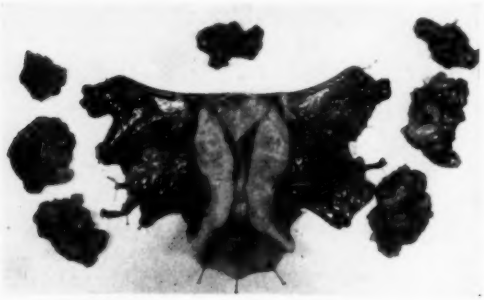

FIG. 3. Surgical specimen.

these 96 patients, but it may be stated that there was no operative death. Up to June 1, 1958, twelve patients had died (Table II). In 9 of these 12 patients the surgical specimens showed metastases to the lymph nodes. The other 3 patients had no metastases, but 1 patient died of pelvic recurrences and metastases to the lungs and retroperitoneal lymph nodes (autopsy), 1 of abdominal metastases (no autopsy), and 1 of bilateral pyonephrosis with no recurrences in the pelvis (autopsy).

UROLOGIC COMPLICATIONS

Neurologic complications of the bladder were seen in most cases for a short period after the indwelling catheter in the bladder had been removed, but in no case was the damage permanent; it disappeared in the first 2 or 3 months. There was no vesicovaginal or rectovaginal fistula.

As to the examination of the upper urinary system, all but 1 patient (who was allergic to iodine) were examined before the surgical treatment. The urograms showed no abnormalities, and only in 1 case was a unilateral hydronephrosis diagnosed. But the latter patient was 3 months pregnant, and the postoperative urograms showed no abnormality. Postoperatively the patients were re-examined between the sixth and the twelfth month, and the urographic findings are shown in Table III. (In the patient with the bilateral pyonephrosis no urography was done.)

There were 4 unilateral ureterovaginal fistulas; 3 of them occurred in the first, and 1 in the fifth month following operation. In 2 of these patients a nephrectomy was done, in the other 2 the fistulas closed spontaneously and left a functionless kidney. One of the patients is now dead.

A. H., 41 years old, had a squamous cell carcinoma. The surgical specimen showed residual carcinoma in the cervix and metastases to right hypogastric, presacral, and left aortic lymph nodes. Postoperative x-ray treatment was given. The right ureter was cut during operation, and consequently ureterovesical implantation was done. A right ureteroabdominal fistula developed in 4 days; the fifth day right nephrectomy was performed. The patient died of uremia 2 years and 1 month after treatment. Autopsy showed metastases to aortic lymph nodes and liver, pyonephrosis and pyemia, and abscess in the spleen.

In 1 patient with no fistula a functionless kidney developed in the postoperative period and was diagnosed by urography 8 months after the operation.

A. M. S. was 49 years old. The surgical specimen showed residual carcinoma in the cervix, carcinoma

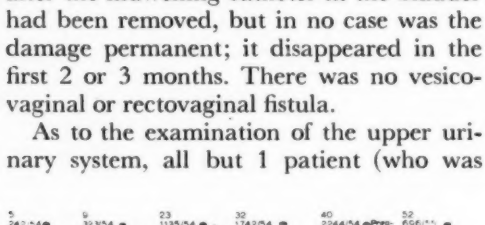

FIG. 4. Location of lymph node metastases. Each spot indicates 1 lymph node with metastases.

TABLE I.—PATHOLOGIC FINDINGS

No. of patients	*Residual tumor in cervix*	*Lymph node metastases*
10	10	0
12	0	12
6	6	6
68	0	0
96	16	18

TABLE II.—RESULTS, JUNE 1958

Year of treatment	*Living*	*Dead*	*Total*
1954	26	5	31
1955	26	3	29
1956	32	4	36
Total	84	12	96

a b c

FIG. 5. Urograms illustrating postoperative "slight hydroureter" on the right side. a, Urogram taken 2 days before operation showing no abnormality. b, Nine months after operation. c, Two years and 8 months after operation showing no progression.

in the left ovary, and metastases to numerous pelvic lymph nodes on both sides. Eight months after operation metastases occurred in the left supraclavicular lymph node. She died of carcinoma 1 year and 3 months after treatment.

One patient died of bilateral pyonephrosis 3 months after the operation.

L. C. M., 35 years old, had no residual carcinoma in the cervix, no metastases to the pelvic lymph nodes. She died of uremia. Autopsy showed no pelvic recurrence, but pelvic hematoma and abscess, bilateral pyonephrosis with ureteral pelvic stenosis and infected pelvic hematoma, and cerebral abscess.

Bilateral hydronephrosis was seen in 4 patients, 3 of whom are now living, while 1 died of recurrences 17 months after the operation.

A. S., 33 years old, had residual carcinoma in the cervix and metastases to the hypogastric lymph nodes on both sides. She died of carcinoma 1 year and 5 months after treatment. No autopsy was performed.

In 1 patient with bilateral hydronephrosis a right ureterovesical implantation was made 6 weeks after the operation, and she has been observed for 2½ years. No recurrences have been noted.

S. A., 28 years old, had no residual carcinoma and no lymph node metastases. Preoperative urography showed no abnormalities, but 14 days following operation the urograms showed bilateral hydronephrosis and hydroureters. The urographic examination was repeated on the twenty-first and the twenty-eighth postoperative days and on the left side showed a retrogression of the hydronephrosis, but on the right side a progression with ureteral stricture in the pelvic part of the ureter. About 6 weeks after the operation she was again operated on, and the right ureter was cut proximally to the stricture and implanted in the bladder. Since then she has several times been re-examined by urography, and the last urograms showed regression of the hydronephrosis on both sides, although still present.

Diagnosis of the hydronephrosis is in some cases difficult because atony of the ureter and of the renal pelvis do not differ very markedly from a slight hydroureter or hydronephrosis. Possibly therefore, some of

TABLE III.—ABNORMALITIES OF UPPER URINARY TRACT IN FIRST YEAR FOLLOWING TREATMENT

	No. of cases	*Total*
Ureteral fistulas	4	
Nonfunctioning kidney	1	
Pyonephrosis, bilateral	1	
Hydronephrosis	5	
Unilateral	1	
Bilateral	4	
Slight hydroureter or hydronephrosis (?)	11	
Unilateral	9	
Bilateral	2	22
No abnormality		69
No postoperative urography		5
Total		96

the 11 patients with slight hydroureter or hydronephrosis have not a pathologic but a physiologic state of the ureter or the renal pelvis. Nevertheless, all these cases have been put down as urographic abnormalities in Table III.

In 69 patients there was no abnormality in the postoperative urograms. Five of these patients are now dead; all of them died of carcinoma.

Unfortunately, it was not possible to carry out urography in 5 patients, 3 of whom are now dead, all of carcinoma.

COMMENT

It is a well known fact that the clinical staging of patients with carcinoma of the cervix is in many cases unreliable, and such is the case with this material too. Metastatic lymph nodes were seen in 18 out of 96 stage I patients, equalling 18.75 per cent. Since Meigs, in stage I patients treated with surgery alone, found positive lymph nodes in 17.5 per cent, there is no evidence in this material that radiation therapy has killed metastatic lymph nodes.

In 1 case 1 metastatic lymph node was seen outside the pelvis (left aortic).

In 12 of the 18 patients with positive nodes there was no residual carcinoma in the cervix, and biopsies of the cervices in these patients may therefore have given a false impression of the prognosis of the disease.

There was no rectovaginal or vesicovaginal fistula.

As to the damage to the ureters, abnormalities of the upper tract were seen in 22 patients, shown by urography 6 months to a year after treatment. Four patients are now dead, 3 having died of carcinoma, and 1 of bilateral pyonephrosis with no sign of recurrences.

It is believed that most of these abnormalities were caused by the treatment given, but in 11 cases the hydroureter or hydronephrosis was slight, and in some cases very slight.

SUMMARY

A series of 96 patients treated with radical surgery and preoperative radiation is presented. There was no operative death. In 18 patients metastases to regional lymph nodes were seen, and in 16 patients there was residual carcinoma in the cervix. In 12 of the 18 patients with positive lymph nodes no residual carcinoma was found in the cervix.

When the possible damage to the ureters was examined by urography, 69 patients showed no abnormality 6 months to a year after treatment, while 22 showed abnormalities as seen in Table III. It is believed that most of the abnormalities were caused by the treatment given, a point which has to be borne in mind when reflecting upon the value of the combined radiologic-surgical treatment.

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CLINICAL EXPERIENCE WITH THE ANTICOAGULANT ANISINDIONE (MIRADON)

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THE USE of prothrombin-depressant drugs is well established in present day therapy. Indications for their use continue to broaden and their general acceptance is steadily increasing. At present the clinician has available to him two main types of prothrombin depressant drugs, those of coumarin origin (dicumarol, cyclocumarol, tromexan, marcumar, warfarin and sintrom) and the indanediones (phenylindanedione and dipaxin). In the selection of an anticoagulant for clinical use the physician is governed first of all by his personal knowledge of the drug selected. Beyond this, the major considerations in such a selection are: (1) ease and rapidity of induction, (2) predictability of the drug's action for long term maintenance dosage, and (3) rate and predictability of recovery from the effects of the drug with or without the use of an antidote. The drugs named vary to some extent in these three characteristics, particularly in the effects which they have upon the rates of prothrombin reduction and of return to normal levels.

This article is presented to describe clinical experience with a new indanedione derivative, anisindione (2-p-anisyl indanedione-1, 3). Earlier reports on the drug have emphasized its rapid action in depressing plasma prothrombin, the stability of prothrombin levels during maintenance therapy, their early return toward pretherapy levels, and the absence of toxic reactions. This water-soluble and tasteless drug is available in 50 milligram tablets for oral use. One hundred five patients were included in the present study. Of these, 64 were observed through induction, maintenance, and recovery, 25 through 75 per cent of their course of therapy, and 16 were being treated at the time of the writing of this article. Periods of therapy varied from 5 to 575 days representing 8,565 patient-therapy days.

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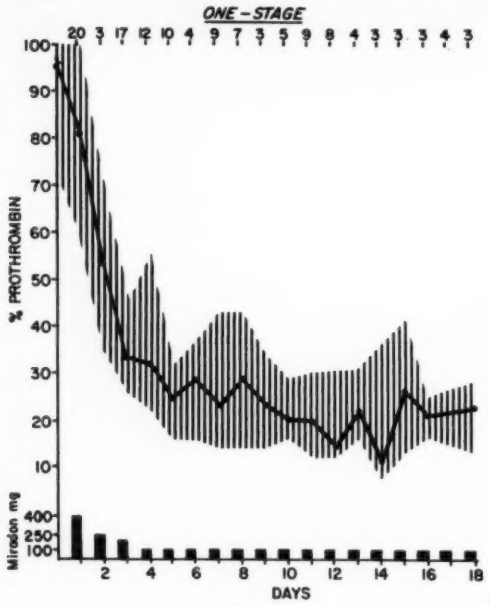
SELECTION OF PATIENTS

The patients were selected from those hospitalized in the Presbyterian-St. Luke's Hospital and the Cook County Hospital, and from outpatients in the Central Free Dispensary of the Presbyterian-St. Luke's Hospital. Volunteers were utilized for special studies. The patients from the Presbyterian-St. Luke's Hospital were selected on the basis of direct clinical indication for anticoagulant therapy. Diagnoses in this group included acute thrombophlebitis, acute myocardial infarction, and rheumatic heart disease with valvular abnormalities, atrial fibrillation, and peripheral-arterial embolism. The patients studied at the Cook County Hospital were selected from the fracture wards. Some of these had evidence of coronary heart disease or thrombophlebitis, but, in general, these patients were given anticoagulants late in the course of fracture healing as prophylaxis against thromboembolic episodes. The patients in the outpatient group of the Central Free Dispensary were administered therapy as indicated. Diagnoses in this group included acute thrombophlebitis, chronic thrombophlebitis, severe peripheral atherosclerosis,



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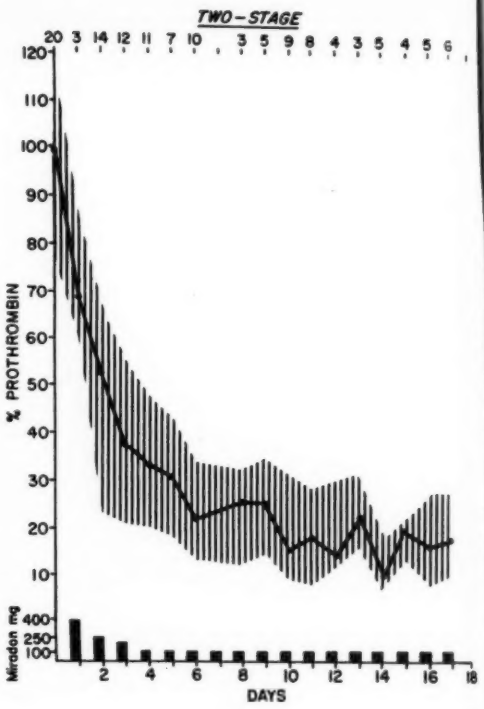

b

FIG. 1. a and b, These graphs represent the composites of prothrombin changes in patients receiving initial doses of 400, 250, and 200 milligrams of miradon on successive days. When these are compared to the courses of the group illustrated in Figure 2a and b, it will be seen that the mean and both extreme levels at 60 hours are not too different. If, however, the graphs are superimposed, one stage on one stage and two stage on two stage, the drop in prothrombin levels is more uniform when the larger doses are used. The figures along the top of each graph indicate the number of patients represented in the mean and extreme points of that particular day. Once the therapeutic level was achieved the prothrombin remained relatively uniform within the desired limits (10 to 30 per cent of normal). It will be noted that the levels appear more uniform in those patients receiving the higher doses originally.

myocardial infarction, peripheral-arterial embolism, cerebral embolism, and rheumatic heart disease with mitral stenosis and atrial fibrillation.

ROUTINE OF STUDY

The routine of study included: (1) measurements of the rate of prothrombin depression, (2) observations on long term maintenance therapy with particular reference to uniformity and reliability of control, (3) measurements of the rate of recovery after withdrawal of the drug, (4) observations on the counter effects of various vitamin K preparations, (5) observations of the effects of the drug on prothrombin accelerator factor V (Ac-globulin, labile factor), and (6) the use of clinical and laboratory means to discover possible untoward reactions to the drug.

LABORATORY METHODS AND MATERIALS

The two syringe technique was used in the collection of all blood samples (1). Parallel prothrombin determinations were carried out by means of the one stage technique described by Quick and the two stage method of Warner, Brinkhous, and Smith, as modified by Ware and Seegers (9). In the one stage technique a commercial thromboplastin (soluplastin) was substituted for rabbit brain extract. In some cases prothrombin was determined by a third method, the TAMe (p-toluenesulfonyl-l-arginine-methyl

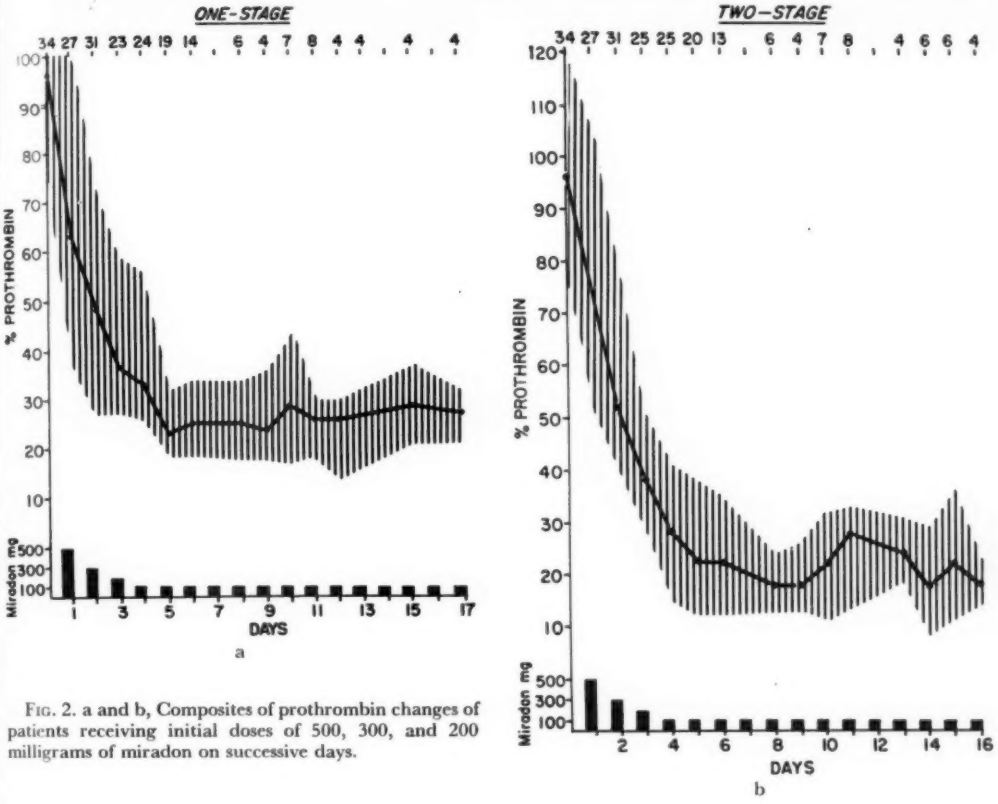

FIG. 2. a and b, Composites of prothrombin changes of patients receiving initial doses of 500, 300, and 200 milligrams of miradon on successive days.

ester) assay, as described by Glueck, Sherry, and Troll. Factor V determinations were carried out by the two stage procedure of Ware and Seegers (8) as modified by Olwin.

ROUTINE OF INDUCTION

In all hospital cases and in most outpatients during the induction period, prothrombin determinations were carried out at 24 and 48 hour intervals. In some cases assays were performed at 8 and 12 hour intervals.

The initial dosage schedule producing optimal effect on the rate and predictability of prothrombin depression was obtained by the administration of varying initial, second, and third doses. In order to obtain more specific data on the effects of a single dose, 6 patients were given doses of anisindione varying from 300 to 700 milligrams and their prothrombin levels were determined as long as an effect of the drug could be demonstrated.

The effect of a single dose of 700, 500, 400, and 300 milligrams was studied in 1 patient for each dose, prothrombin levels being determined daily. In addition, the effects of 500 milligrams given as a single dose were observed in 2 patients at 12 hour intervals.

MAINTENANCE THERAPY

In the majority of the hospital patients, the effectiveness of control in the maintenance phase was determined by daily prothrombin assays. This procedure was continued throughout the entire hospital

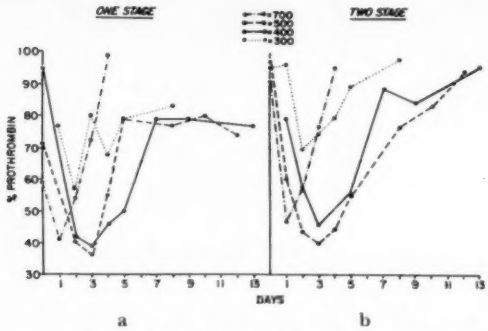

FIG. 3. a and b, The prothrombin changes in individual patients receiving 700, 500, 400, and 300 milligrams of miradon as single doses. It will be noted that while in the one receiving 700 milligrams there was a slightly more rapid drop in prothrombin, the degree of suppression was not as great as in the patients receiving 500 and 400 milligrams each. The effect in the latter 2 patients was also more prolonged. As with other prothrombin-depressant drugs, the pattern of prothrombin drop and recovery is more uniform as measured by the two stage method than by the one stage.

stay. Some of the patients followed up in the Central Free Dispensary were those previously discharged from the hospital but still continuing anticoagulant therapy. Others who were given therapy as outpatients were tested at 48 hour intervals at the beginning of therapy, then at 4 day intervals, 7, 14, and, in a few instances, at 21 day intervals as indicated by their respective prothrombin levels. In order to determine whether or not a single daily dose was adequate to maintain control levels, prothrombin assays were made at 12 hour intervals in 4 patients after therapeutic levels had been attained. In these patients daily doses of the drug were first given and later the same maintenance doses were split, half of the former daily dose being given at 12 hour intervals.

The period of therapy of the entire outpatient group ranged from 3 weeks to 19 months. To 2 patients who had been well controlled on a daily dose, larger doses (250 mgm.) were given at somewhat longer intervals (every third day) in order to evaluate this method of administration of the anisindione.

ROUTINE OF OBSERVATION DURING RECOVERY

After withdrawal of the drug in most hospitalized patients not given antidotes, prothrombin levels were measured at 24 hour intervals. In the case of some outpatients the same routine was followed, whereas in others this interval was extended to 48 or 72 hours. Five patients observed without antidote administration were tested at 8, 12, and 24 hour intervals to determine more accurately the rate of recovery.

The effects of antidotes given at intervals varying from 12 to 36 hours after the last regular dose of anticoagulant were studied. This routine was carried out in 9 patients following the administration of water-soluble vitamin K (K_3) intravenously and in 3 patients following the administration of 50 milligrams of fat-soluble vitamin K (K_1), mephyton, by the same route. Six patients were given 50 milligrams of fat-soluble vitamin K (K_1) orally and 5 patients were given smaller doses (10 or 15 mgm.) of the same substance.

OBSERVATIONS ON GENERAL PHYSIOLOGIC EFFECTS

During the first 8 months of the study all patients from the Central Free Dispensary (24) were given periodic physical examinations at intervals ranging from 2 to 6 weeks. In addition, urinalyses, hemoglobin determinations, and leucocyte and differential counts were done. Bone marrow examinations were carried out in 5 patients after periods of 2 to 12 months of therapy. In 8 patients, liver profiles which consisted of 2 or more of the following determinations were obtained: bilirubin, bromsulphalein excretion, total plasma protein, plasma albumin, plasma globulin, and cephalin flocculation.

RESULTS

Behavior of prothrombin levels during induction. At the beginning of the study patients were given 300 milligrams of anisindione following the initial prothrombin determination. Two hundred milligrams were given

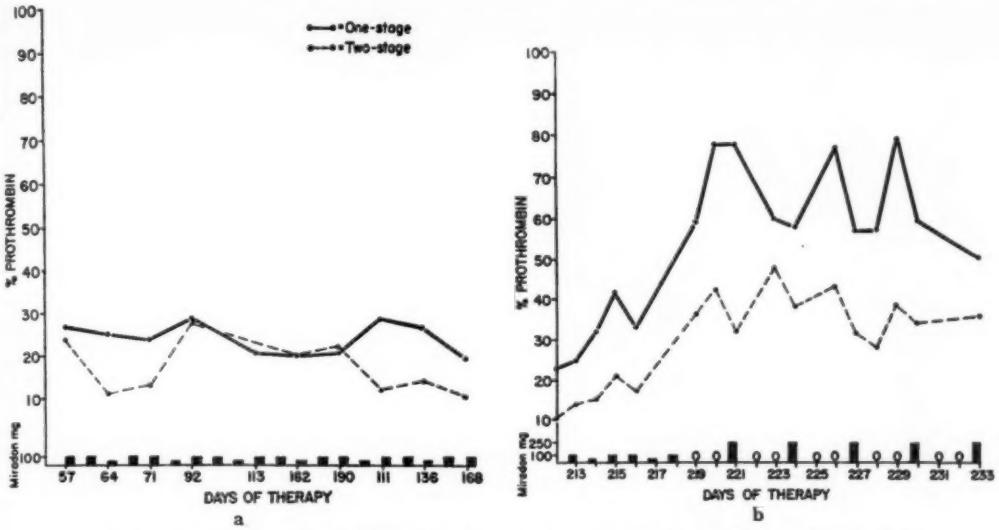

FIG. 4. a, The course of a patient who was maintained continuously for 213 days on a regularly repeated 3 day schedule of 100, 100, and 50 milligrams of miradon with no "escape" from the therapeutic bracket during this period. b, The prothrombin levels of the same patient after a change of dosage schedule to 250 milligrams each third day. Immediate "escape" occurred and persisted as long as the alternate dosage was continued.

on the second day and 100 milligrams on the third day. Ten patients were given this sequence of doses and, although it was noted that satisfactory control (30 per cent or less as determined with the two stage assay) was approached on the third day by 2 patients, 6 patients required 5 or 6 days to achieve this level.

The next dosage schedule was one of 400 milligrams on the first day followed by 250 and 200 milligrams on the second and third days respectively. The effects of this schedule were observed in 20 patients and the results obtained are shown in Figure 1a and b. The mean prothrombin level on the third day of therapy (60 hours) was 33 per cent by the one stage method with a range of 26 to 45 per cent, and 37 per cent by the two stage with a range of 21 to 55 per cent. In addition to the data which are illustrated in the graphs, it can be stated that 90 per cent of the patients in this group achieved prothrombin levels below 30 per cent by both the one and two stage tests by the fifth day of therapy (108 hours).

During the latter part of the study, a regimen of 500 milligrams on the first day, 300 on the second, and 200 on the third day was employed in 36 patients. Data on this group appear in Figure 2a and b. It is apparent that on the third day of therapy (60 hours) the mean prothrombin levels were 36 per cent with a range of 27 to 59 per cent by the one stage and 38 per cent with a range of 28 to 51 per cent by the two stage. On the fourth day (84 hours) the one stage was 33 per cent with a range of 21 to 56 per cent and the two stage, 28 per cent with a range of 14 to 40 per cent. In this group 1 patient required 6 days to achieve effective control. All others required less time, and in the majority control was achieved by the third or fourth day of therapy.

In 2 patients who were given a still higher initial dosage (700 and 300 mgm.) there was no appreciable increase in the rate of prothrombin suppression.

The effects of single doses are represented in Figure 3a and b. It is apparent that in the entire range of single doses used the

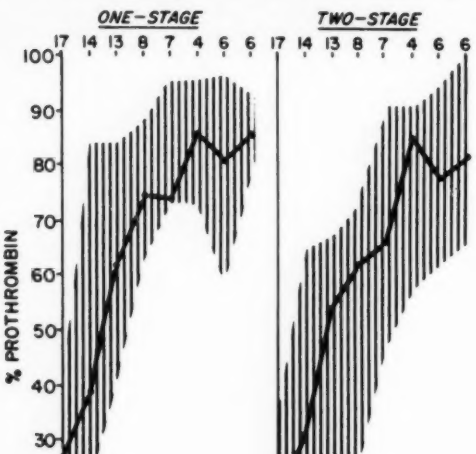

FIG. 5. a and b, The changes in prothrombin levels after withdrawal of miradon. Day 0 on the graph represents the day of discontinuance (12 hours after the last dose). Day 1 represents a point 36 hours after the last dose when the prothrombin was 38 per cent as measured by the one stage method and 31 by the two stage. In 60 hours after the last dose the average prothrombin was 62 and 54 per cent, respectively, and by 84 hours 74 and 60 per cent. As in Figures 1 and 2 the two stage curve lags slightly behind the one stage. This same phenomenon has been observed with all prothrombin depressants.

nadir of the one and two stage prothrombin curves is reached at a point between 36 and 50 hours after the administration of the drug. The prothrombin in most instances returned to predrug, or near predrug, levels by or before the seventh day. A single dose of 700 milligrams, while producing a somewhat more rapid fall, did not result in a greater prothrombin suppression than did a single dose of 500 milligrams. The effects of 500 and 400 milligrams were approximately the same. The 300 milligram dose was less effective.

The dosage schedule of 500 milligrams on the first day, 300 on the second day, and 200 on the third followed by daily dosage as indicated by prothrombin levels appeared to be the most satisfactory. In all cases studied satisfactory control was eventually obtained, this being achieved in the majority of patients on the third or fourth day and, in some instances, as early as the second.

Maintenance therapy. Once the prothrombin levels had been reduced to the therapeutic bracket, they were maintained there with little difficulty on daily doses of the drug (Fig. 1 and 2). In 4 patients the individually established daily dose was divided and half given at intervals of 12 hours. The prothrombin levels determined at 12 hour intervals were essentially the same under both routines. The dose required in order to maintain the patients at control levels ranged from 50 to 150 milligrams per day.

Interval dosage. As noted before, 2 patients who were satisfactorily controlled by daily dosages of anisindione were selected for a trial with larger dosages of the drug at 3 day intervals to determine the comparative effectiveness of this method of administration. One of these patients had been effectively controlled for 5 weeks, the other for 10 months. Both patients were studied as follows: for the week prior to the change from daily therapy to the longer interval the patients were requested to continue their old regimen and to report to the laboratory daily, Monday through Friday, for prothrombin determinations. They were then routinely given 250 milligrams of anisindione every third day and were requested to continue coming to the laboratory daily, Monday through Friday, for the first 2 weeks of the period during which they were on this program. Patient 1 was kept on the latter regimen for 4 weeks during which time her therapy was not effectively controlled. Her prothrombin at the end of this time was 53 per cent by the one stage method and 56 per cent by the two stage. Similar variations occurred in patient 2 (Fig. 4a and b). Based on our observations

of these 2 cases it is our opinion that of the two methods discussed, daily administration of the drug provides for greater uniformity of control. In this respect our experience differs from that of Lange and associates.

Recovery. Data representing the course of 20 patients observed during the recovery phase are shown in Figure 5a and b. It is apparent from these results that 12 hours after the withdrawal (36 hours following the last regularly administered dose) the average prothrombin had risen to 62 per cent as measured by the one stage method and to 54 per cent by the two stage. Five patients not included in this graph were observed at intervals of 8, 16, 24, 32, 40, 52, 64, and 88 hours after the last regularly administered dose of the drug. The data on these 5 patients are shown in Table I, and a graph of representative prothrombin changes observed on 1 of them is shown in Figure 6. In all of these patients the prothrombin shows an abrupt rise beginning either 32 or 40 hours after the administration of the last regular dose of miradon, the prothrombin being above the therapeutic bracket within 40 hours in 3 patients, and within 48 hours in all patients.

The effect of vitamin K preparations on the recovery rate. The effect of vitamin K preparations on the recovery rate was studied in 23 patients. In 6 patients who were given 50 milligrams of fat-soluble vitamin K (K_1) by mouth an abrupt rise in the prothrombin level (in some instances from 25 to 45 per cent within 6 hours) was apparent when the vitamin preparation was given during the maintenance phase. A sharp rise also occurred when the vitamin was given during induction simultaneously with or shortly after the administration of a large dose of the anticoagulant. In the 3 patients who were given 50 milligrams of intravenous fat-soluble vitamin K a rise to 50 per cent or more on the one and two stage prothrombin levels was noted within 1 hour. Comparable

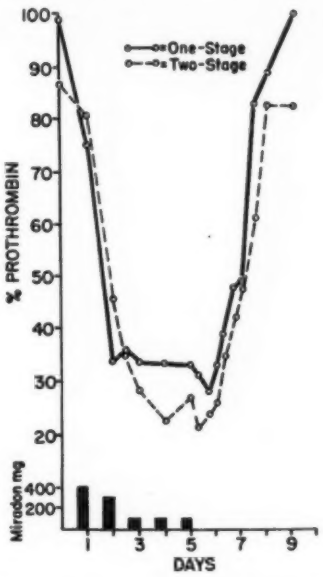

FIG. 6. This graph represents the course of a patient whose recovery course was followed with prothrombin assays at 8, 16, 24, 32, 40, 52, 64, and 88 hours after the last regularly administered dose of the drug. By 32 hours the prothrombin level by both tests was above 30 per cent and the rise from that point was at a rapid rate.

TABLE I.—DATA ON 5 PATIENTS

Hours after last dose	*Patient 1*		*Patient 2*		*Patient 3*		*Patient 4*		*Patient 5*	
	One stage	*Two stage*	*One stage*	*Two stage*	*One stage*	*Two stage*	*One stage*	*Two stage*	*One stage*	*Two stage*
0	28.5	18.6	33.0	26.9	29.0	18.4	28.0	29.9	28.0	20.8
8	24.0	16.9	31.0	21.2	32.0	17.2	29.0	22.3	27.0	19.0
16	22.0	14.9	28.0	23.7	28.0	17.3	29.0	26.3	30.0	20.9
24	27.0	20.1	33.0	25.8	33.0	23.2	31.0	26.0	26.0	20.9
32	32.0	28.8	39.0	34.8	35.0	28.7	30.5	26.0	26.5	22.8
40	41.0	43.0	48.0	42.4	40.0	29.8	33.5	30.3	28.0	23.6
48	40.0	46.0	49.0	47.9	44.0	34.8	33.0	37.1	35.0	39.0
60	54.0	59.7	83.0	61.5	56.0	44.2	55.0	42.9	54.0	47.8
72	67.0	66.7	89.0	83.0	57.0	51.3	62.0	67.5	59.0	54.5
96	80.0	72.0	100.0	82.6	85.0	54.6	85.0	74.7	85.0	73.1
168	55.0	101.5			55.0	81.2			65.0	121.2

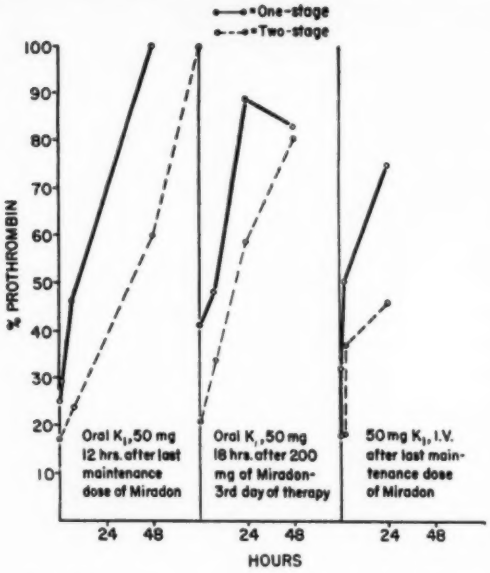

FIG. 7. These graphs represent the changes in prothrombin levels of patients recovering from miradon therapy after receiving large (50 mgm.) doses of fat-soluble vitamin K (K_1)—orally or intravenously. In all patients studied there was an acceleration of the prothrombin rise as compared to that of patients receiving no antidote and those receiving small doses of K_1 and large doses of K_3. In view of the rapid recovery rate following withdrawal of miradon therapy, vitamin K is rarely necessary. When it is indicated, however, 50 milligram doses of the fat-soluble preparation are recommended.

1 hour readings were not obtained on the patients who received oral fat-soluble vitamin K. Representative changes in prothrombin levels of each of these three groups are shown in Figure 7.

In the 9 patients who were given 72 milligrams of water-soluble vitamin K (K_3) intravenously at varying intervals after withdrawal of the anticoagulant and in the group of 5 patients who received 10 or 15 milligrams of vitamin K_1 orally the rate of recovery was not accelerated over that observed when no antidote was given. Representative responses of these patients are shown in Figure 8. It is recognized that these two groups are too small to allow definite conclusions, but the results obtained would suggest that the usual clinical dose of water-soluble K and the smaller dose of fat-soluble K, when given orally, are without clinical effect.

Effect on plasma Ac-globulin. Ac-globulin determinations were carried out on the plasma of 2 patients through induction and recovery. As a result of anisindione therapy, the plasma concentration of this factor was decreased to levels between 25 and 50 per cent of normal within 4 to 5 days following initiation of therapy. After withdrawal of the drug, the level of Ac-globulin returned to normal at approximately the same rate as the prothrombin, as measured by the one stage method.

Observations on the use of the TAMe assay. The TAMe assay for prothrombin was performed in parallel with the two stage test on the plasmas of 20 patients. Five of these were followed through induction and recovery while the remaining 15 had only spot determinations. This series involved 175 duplicate determinations and the results closely paralleled those of the two stage test (Fig. 9). This observation supplements an earlier report of a similar relationship of the results of the two assays carried out on patients treated with 8 other prothrombin depressants (2).

Toxic effects. Systemic effects in patients undergoing long term therapy, as evaluated by bone marrow aspiration, peripheral blood examination, urinalyses, and liver function tests as enumerated, were not observed.

Incidence of hemorrhage. In the entire series 6 patients (5.7 per cent) exhibited bleeding phenomena. These consisted of gross hematuria in 2 patients (investigation revealed in 1 a history of hematuria prior to therapy which the patient had not disclosed on previous questioning), minimal epistaxis in 2 patients, and significant epistaxis with purpuric phenomena in 1 patient. In 1 patient a tooth socket continued to bleed following a tooth extraction while the patient was receiving controlled therapy. No unfortunate results attributed to bleeding were encountered in the series.

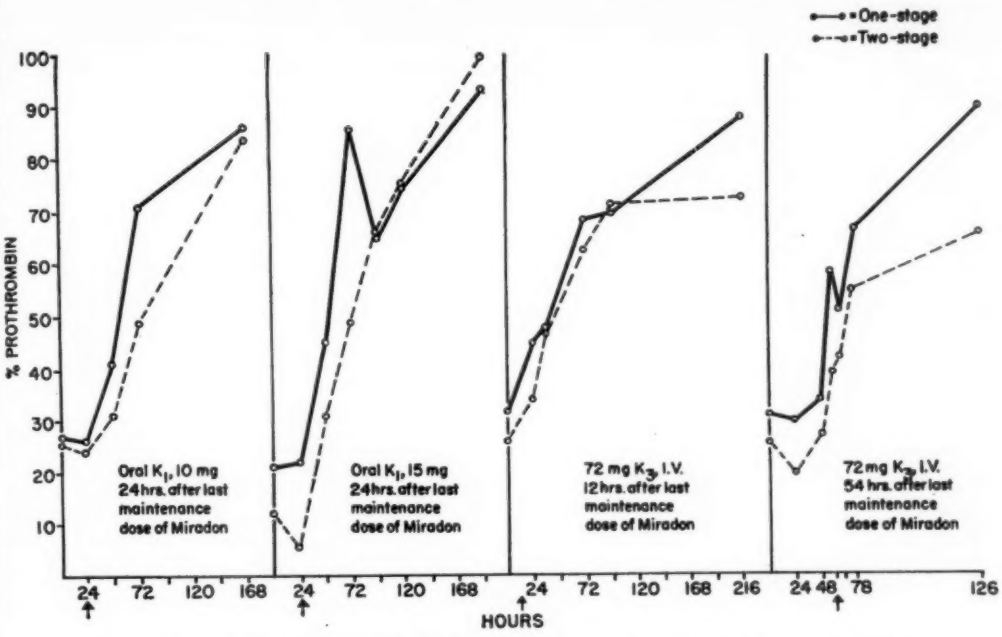
One-stage
Two-stage
% PROTHROMBIN
100
90
80
70
60
50
40
30
20
10
Oral K1, 10 mg 24 hrs. after last maintenance dose of Miradon
Oral K1, 15 mg 24 hrs. after last maintenance dose of Miradon
72 mg K3, I.V. 12 hrs. after last maintenance dose of Miradon
72 mg K3, I.V. 54 hrs. after last maintenance dose of Miradon
24 72 120 168 24 72 120 168 24 72 120 168 216 24 48 78 126
HOURS

FIG. 8. These graphs are representative of the effects of small oral doses of fat-soluble vitamin K (K_1) and large intravenous doses of water-soluble K (K_3) on depressed prothrombin levels. No appreciable difference was noted in the change in prothrombin levels when compared to changes in patients receiving no antidote.

Chromaturia. Chromaturia is defined here as a reddish or pink coloration of the urine present in the absence of gross or microscopic hematuria. Lange and his associates observed no instance of this phenomenon; Blaustein reported it in several patients, though to a lesser degree than in patients receiving phenindione. The appearance of such "red urine" was frequently observed by patients at the beginning of therapy and occurred almost exclusively on the second and third days. Microscopic hematuria could not be detected in samples of freshly voided urine or urine which had been kept refrigerated, and it was noted that in many of the specimens the pink coloration disappeared following standing of the urine samples at room temperature for a number of hours.

More detailed observations of this phenomenon were made through the co-operation of two physician volunteers who received anisindione in conjunction with another phase of this study. Both of these observers noted no change in the color of urine voided during the first day of therapy although toward the end of the second day their specimens became progressively darker. On the third day the urine had a definite red coloration. It was noted by one of these observers that the red color was particularly intense when the urine was more highly concentrated and that a normally colored urine specimen could be obtained within a period of 1 or 2 hours by drinking copious amounts of water.

Acidification of chromaturic urine (*p*H 6.3) resulted in the disappearance of the red color at a *p*H of 4.2, whereas the addition of alkali up to *p*H 12.0 had no effect on it. Shaking of normal urine with anisindione also produced a reddish coloration, an effect not observed when the drug was added to 0.5 normal hydrochloric acid.

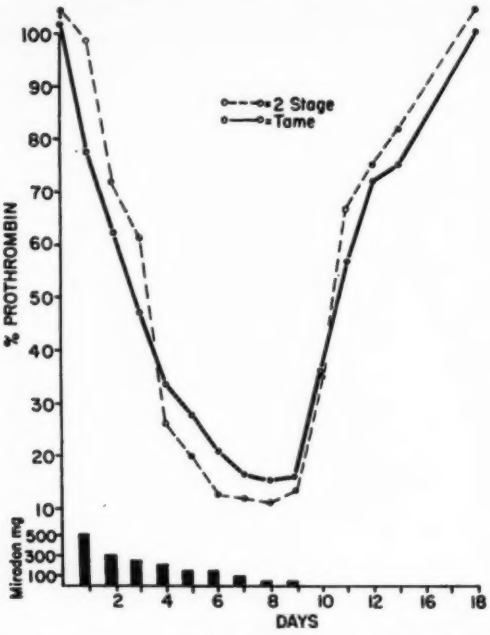

FIG. 9. The course of a single patient given miradon through induction, and recovery as measured by the two stage and the TAMe prothrombin assays. The closely parallel results seen in this graph are similar to those observed in 19 other patients on whose plasmas the two tests were run.

It is of interest that no chromaturia was observed once maintenance therapy with anisindione was well under way. It would appear that the occurrence of this phenomenon during the induction phase only may be related to a temporary hyperconcentration of the drug in the blood stream at this time. This assumption is supported by the observations (a) that the chromaturia disappears when the dosage levels are reduced and (b) that the same effect can be produced by the intake of large amounts of water. This latter, together with the disappearance of the red color by dilution of the urine or allowing it to stand at room temperature, will readily distinguish the chromaturia from hematuria. It is emphasized again that the chromaturia appears at a time in therapy when the prothrombin is well above ordinary bleeding levels.

Patients placed on anisindione were forewarned of the possibility of such a color change in the urine in order to avoid possible anxiety about it.

SUMMARY

1. Anisindione (miradon) was administered to 105 patients with and without thromboembolic disease.

2. Anisindione was found to be a safe and effective prothrombin depressant, therapeutic levels being attained on the second, third, or fourth day in the majority of patients. The shortest period of induction observed was 48 hours.

3. The dosage schedule of 500 milligrams on the first day, 300 on the second, and 200 on the third followed by daily dosage as indicated by prothrombin levels appeared to be the most satisfactory. The dose required to maintain patients at control levels ranged from 50 to 150 milligrams per day, given as a single dose.

4. Following withdrawal of the drug prothrombin levels rose to above 30 per cent of normal in 36 hours in most cases. The shortest period observed for such rise was 18 hours. Sixty per cent prothrombin levels were observed 60 hours after the last dose of the drug was given.

5. Return toward normal prothrombin levels was accelerated by intravenous administration of fat-soluble vitamin K substances.

6. In addition to its effect on prothrombin, anisindione was observed to depress the level of plasma Ac-globulin.

7. The TAMe (p-toluenesulfonyl-l-arginine-methyl ester) method for prothrombin assay was found to be well suited as a means for controlling the administration of anisindione.

8. Liver function tests and bone marrow studies gave no evidence of toxic effects in patients receiving the drug over periods of time ranging up to 12 months.

9. Bleeding was observed in 6 patients. In no instance was this found to be of a serious nature.

10. Chromaturia was observed as a side effect during the early phases of therapy. This is related to the amount of drug administered rather than to a low prothrombin level. Several simple observations can be carried out by the patient to distinguish it from hematuria.

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CARCINOMA OF THE CERVIX

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IN RECENT YEARS great interest has developed as to the proper method of treatment for carcinoma of the cervix. Years ago surgeons and gynecologists struggled to perfect both the abdominal and the vaginal approach for removal of the cancer and its areas of spread. Later, with the advent of radium and roentgen therapy, the surgical attack was forgotten except in a few European clinics. In 1934 Taussig of St. Louis demonstrated the importance of the transperitoneal removal of the pelvic lymph nodes. Following his conception of the method of removal of the nodes it was obvious that the next step would be the renaissance of the Wertheim operation plus routine removal of the nodes by Taussig's method of dissection. At this point the development of better methods of blood transfusion and the discovery of the sulfonamides and the antibiotics pointed to the possibility of the safety of radical pelvic surgery. Thus it was certain that the surgical attack would again be undertaken. It was easily demonstrated that radical surgery could be carried out safely with almost as low a mortality as with radiation therapy. With this type of surgical operation there is a possibility of causing urinary tract complications in a fairly high percentage of cases. The possibility also exists of destroying the patient's sex life because of shortening the vagina.

Because of the dearth of positive lymph nodes in patients with small cancers, Friedell and Graham analyzed 40 cases of cancers of 1 centimeter or less in size and found no lymph node metastases. From reading their article in this journal (p. 513), it is possible that from the evidence surgeons will interpret that all that is necessary to cure patients with this early type of cancer is to do a simple total hysterectomy. This I believe to be wrong, for, although the nodes may not be involved, the lymphatic channels in the cervix itself and in the tissues about the cervix and vagina, the so-called parametrial tissue, have not been proved to be involved or not involved by extending cancer. In their series the patients have had radical surgery and the parametrial areas have been removed but not thoroughly investigated. We do not know whether these areas are involved or not. The patients have been "cured"; but is that due to the fact that the lymph channels were not involved or because these areas had been carefully extirpated? This editorial has been written to point out the fact that until we have proof that the cervical and parametrial lymph channels are not involved in very early cancer of the cervix we should not rely upon simple total hysterectomy. Perhaps the routine lymph node dissection need not be done but the old Wertheim operation, with removal of the paravaginal and paracervical tissues and their lymphatics and a good vaginal cuff, should be the operation of choice and not the newer more radical operation in vogue at the present time. It is much easier and less dangerous to do a simple total

hysterectomy but in all probability that operation is not sufficient. We must revise our techniques whenever newer knowledge indicates. I believe that the lymph node data in this narrow group give no information on the need for or against radical hysterectomy.

I have been distressed by a small but steady stream of patients coming to our clinics with residual or recurrent cancer following inadequate surgery. It would be unfortunate if that stream were to increase from misinterpretation of this article. Radical surgery has been of inestimable value in the understanding of cervical carcinoma. It is fortunate that it offers the means of study that may make possible reduction in the extent of operation required in certain types of patients. It behooves us as surgeons and pathologists to make use of this material to that end.

The article by Friedell and Graham is timely and important, but it must not be interpreted to mean that total hysterectomy is the procedure of choice for even the smallest invasive cancer of the cervix.

CANCER HETERODOXY

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PROMULGATION of new concepts usually connotes dissatisfaction with existing beliefs. Surely, there is less than universal satisfaction both with the current management of visceral cancer and, more significantly, with the relatively limited advances during the recent past. Of more than incidental interest is the observation that the finite progress has primarily resulted from investigations other than those chiefly concerned with the problem of cancer. Fundamental developments in related and unrelated physical and biologic sciences have been adapted and utilized in the treatment of cancer. While this is not to minimize nor denigrate this usurpation, the implications demand recognition.

Increasing and expanding surgical heroism has become possible primarily because of the great advances in our understanding of electrolyte metabolism. Similarly, immunologic advances have made it possible to utilize blood therapeutically to a degree wholly unanticipated even a decade ago. Surgical intervention is now feasible in patients previously considered poor risks at best. In the vigorous, the limits of extirpative procedures are frequently the anatomic borders of body cavities. Despite this increase in the size of the therapeutic reservoir and the depths to which it may be probed, the anticipated corollary of a parallel improvement in end results has yet to materialize. Radiant energy for the treatment of neoplastic disease is now available at megavoltage levels. Entirely convincing data are still lacking to prove that ultrahigh energy sources of irradiation are more efficacious in the treatment of cancer than is the modern orthovoltage unit in the hands of a competent radiotherapist. The disappointing experience accompanying the incorporation of this newer knowledge in cancer therapy emphasizes the impoverished state of pure orthodoxy in both thought and action.

Early diagnosis is a third pillar on which orthodoxy is perilously perched. Along with supervoltage x-ray and superradical surgery, admitted minor improvements in end results have occurred; regrettably, they have apparently reached a plateau. Hammond, in discussing the effect of early diagnosis in improving the over-all survival rate in cancer, concluded, "There is reason to believe that some improvement in the over-all survival rate may yet be made through earlier diagnosis. However, it appears that a point of diminishing returns has been reached. If so, only limited room remains for further advances by this means with techniques now at hand. This does not imply that efforts for early diagnosis should be relaxed, since in that event the benefits already achieved might be lost."[1] Orthodox management of visceral cancer even under ideal conditions is rapidly nearing the apogee in possible end results.

Those of us concerned with experimental as well as clinical cancer are dismayed that research primarily oriented to the problems of growth has contributed little toward improving end results; nevertheless, we recognize that amelioration of any situation necessarily begins with its true assessment. Biologic predeterminism is but one attempt to characterize the problem. It is sad that the phrase has developed a "that man" connotation of derision to those who regard the questioning of traditional concepts as wholly sterile. Biologic predeterminism recognizes the obvious—each neoplasm is endowed with a natural history all its own. Endogenous and probably exogenous factors

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unite to form the constellation of cancer inception, clinical course, and prognosis. Ideally, the aim of treatment should be the creation of an internal environment incompatible with either initiation or survival of the new growth. Research in the biologic sciences is making progress to this end. In the interim, the judicious use of radiation and surgical intervention in the treatment of cancer is applauded and employed by the "heretics." Therapeutic nihilism has no place within the concept of biologic predeterminism. The latter simply deplores the unwarranted and unsupportable contention that increased energy and exuberance in the implementation of treatment carries with it the inevitability of increased benefits. While rejecting this false assurance, predeterminism frequently offers hope rather than despair. It eagerly seeks to identify and characterize indolence in neoplastic growth. Systemic host factors as well as the neoplasm itself should be scrutinized for the bases of good prognosis. Orthodox methods in the diagnosis and treatment of cancer though used are recognized as being tangential in approach.

The present status of cancer therapy recalls the level of treatment of infectious disease in the premicrobiologic era. Before the advent and availability of sera, toxins, vaccines, and chemotherapeutic agents, not all patients with so-called "fatal" infectious disease died. Indeed, the use of poultices, bleeding, and other now abandoned procedures was credited with cures. May not the treatment of cancer be in an analogous situation today? Milestone accomplishments did not result from experimental efforts aimed at producing hotter poultices or more efficient methods of venesection. Rather, the concepts of the bacterial origin of disease and prophylaxis through immunization resulted from the unorthodox thinking. The roots of heresy in both thought and action traditionally find fertile soil in the debris incidental to the failure of orthodox beliefs.

Dismissal or rejection of newly introduced fundamental concepts because of possible misapplication by the ignorant or incompetent is myopic and dangerous. It is inconceivable that the average surgeon's faith in his capacity to treat a patient is so tenuous and labile that the responsible questioning of traditional concepts would result in a nullification of his professional and social usefulness. The denotation of past failures and future limitations within the current concept of authority need not have as its sequel anarchy. In medicine, successive orthodoxies have been the heterodoxies of yesteryears.

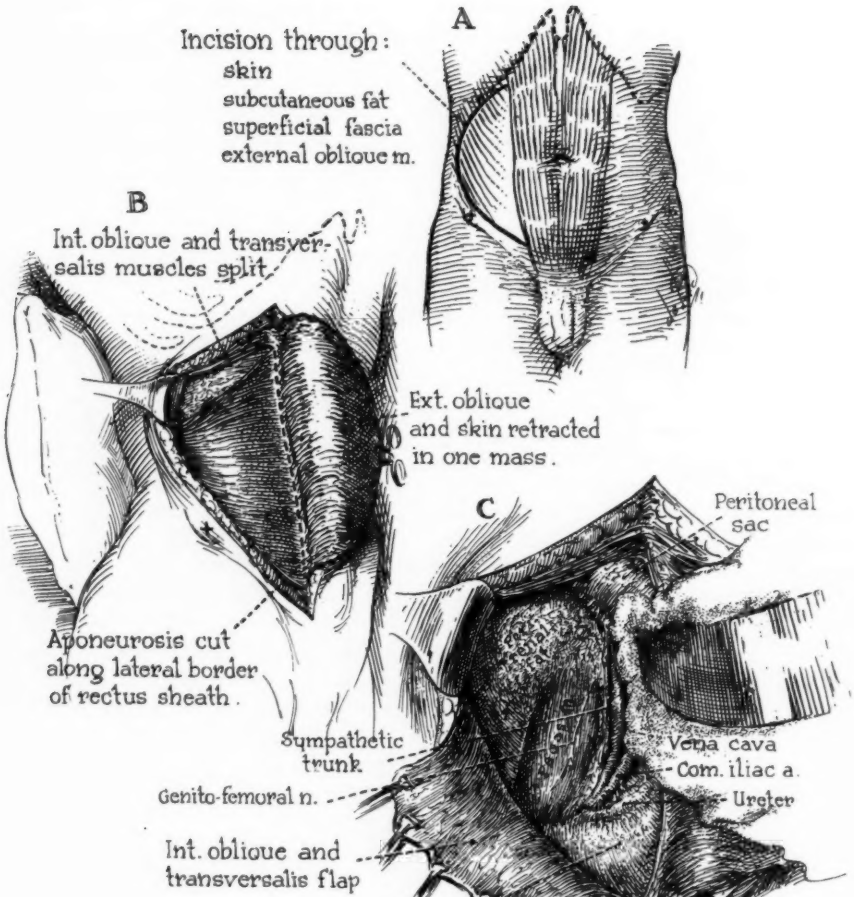

FIG. 1. A, A crescentic incision is made lateral to the rectus muscle sheath. B, The configuration of the incision makes it possible to reflect the superficial structures medially. The aponeuroses of the internal oblique and transversalis muscles are incised along the lateral border of the rectus sheath. C, The retroperitoneal structures are adequately exposed by retracting the peritoneum and its contents.

An Improved Incision for Retroperitoneal Exposure.—Frederick G. Stoesser.

THE SURGEON AT WORK

AN IMPROVED INCISION FOR RETROPERITONEAL EXPOSURE

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AN INCREASE in the number of extensive operations upon retroperitoneal structures makes almost mandatory an operative approach that will expose these structures adequately without sacrificing the strength or function of the abdominal wall. While lesser procedures, such as sympathectomy, can be done through a small muscle-splitting incision, such operations as arteriectomy, or nephrectomy with removal of the entire ureter, demand an exposure that will make the operative procedure easier and less hazardous. With this in mind, I started with the Ochsner modification of a LaReche incision for sympathectomy, making certain modifications and additions to it that allow exposure of the entire retroperitoneal structures of the right or left side.

A crescentic incision is made lateral to the rectus muscle sheath, starting just below the costal margin and extending outward to the lateral edge of the abdominal wall, then curving inward and downward, parallel to the inguinal ligament, and ending at the lateral border of the rectus muscle sheath (Fig. 1A). The incision penetrates the skin, subcutaneous fat, superficial fascia, and the fibers of the external oblique muscle and its aponeurosis, making it possible to reflect this mass of tissue medially to the rectus muscle sheath, where it is held in position with a towel clip or Allis clamp (Fig. 1B). The weight of the clamp prevents the tissue from falling back over the internal oblique muscle.

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At or near the upper margin of the incision, the internal oblique and transversalis muscles are split in the direction of their fibers, about 1 inch from the costal margin. It is important to start this muscle separation well laterally in order to prevent entering the peritoneum, because in the lateral region of the abdomen there is considerably more properitoneal fat between the peritoneum and the muscle than there is near the edge of the rectus muscle sheath. If these muscles are separated close to the rectus muscle sheath, the peritoneum will be penetrated and the defect must be closed immediately. The aponeuroses of the internal oblique and transversalis muscles are incised along the lateral border of the rectus sheath, as shown in Figure 1B. A number of moderate-sized vessels are necessarily severed when this is done. They must be clamped and ligated immediately to prevent a bloody field. The peritoneum and its contents are then pushed medially and held out of the way by means of a heavy abdominal gauze pack and a Deaver retractor (Fig. 1C). In addition, the table is tilted away from the operator in order to take advantage of the effect of gravity.

By this incisural technique, the kidney and the entire ureter can be exposed and complete removal accomplished; a ligated or severed ureter can be implanted into the bladder; the aorta and the iliac artery can be exposed and resected; the iliac vein can be ligated; the vena cava can be ligated; and the sympathetic nerves of the lumbar region can be removed. The incision can be extended down over the femoral canal for operative procedures involving vessels

in this region or for exposure or operation upon the aorta. This type of exposure can also be used for inlay bone grafts to fuse the bodies of the lumbar vertebrae from an anterior approach.

Although occasions demanding such an extensive approach do not often arise for the general surgeon, it is well to have some means of providing adequate exposure of retroperitoneal structures when it does become necessary. I have used this approach 20 or more times in the past 10 years and have found it most helpful.

Reconstruction of the incision is carried out with meticulous anatomic apposition to prevent weakness of the abdominal wall. The aponeuroses of the internal oblique and transversalis muscles are sutured to the edge of the rectus sheath from below upward, after which these muscles are approximated along the line of the split in their fibers. This step is carried out with a nonabsorbable material, usually cotton. The aponeurosis of the external oblique muscle and the muscle itself are then approximated to their adjacent edges along the line of the crescentic incision, using interrupted cotton, and the remainder of the incision is closed in layers with fine cotton sutures.

RESULTS

There was no instance of wound infection or herniation, as proved by follow-up examination, in any of the patients on whom this incision was used.

Even though the intercostal nerve supply to the lower portion of the rectus abdominis muscle is severed by this technique, there has been no failure of function of this muscle. This fact is undoubtedly due to the enervation at its upper end through intercostal trunks which have not been severed.

There has been no bulging of the flank on the side where the incision was made, and there was little complaint of discomfort on the part of patients subjected to this incision.

The strength of the abdominal wall on the side of the incision, following healing, appeared to be equal to that of the opposite side.

SHOULD ANTIBIOTICS BE USED IN LARGE BOWEL PREPARATION?

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FOR MANY YEARS, surgeons have tried to improve the method of preparing the large bowel for surgery. The advent of modern chemotherapy resulted in a marked acceleration of research in this field as a continual succession of new antimicrobial agents appeared, each reputedly better than its predecessors. Unfortunately, the "sterile bowel" promised by the proponents of these agents fails to materialize when they are subjected to careful analysis. And, in the pursuit of this will-o'-the-wisp, the fundamental principles of bowel preparation are too often neglected. Furthermore, commercial promotion with its attendant pressure upon investigators has tended to overcome sound medical judgment and results in misuse of valuable drugs to the detriment of patient welfare. With these thoughts in mind, it is our purpose to present the case for the primary importance of mechanical cleansing in the preparation of the large bowel for surgery. In so doing, we draw upon our 5 to 6 year study in intestinal antisepsis, involving more than 200 hospitalized adult patients. Although our research on intestinal antisepsis included more than just the preparation of the large bowel for surgery, we will limit this discussion to that subject. Our objectives were: (1) to have the large bowel clean and empty at the time of surgery, (2) to achieve a sterile or near sterile bowel, (3) to do so within a 24 hour period, (4) to maintain the state of sterility or near sterility for at least 1 to 2 days, (5) to be able to repeat this antiseptic procedure successfully in the same patient within a few days, and (6) to produce these effects with minimal irritation of the bowel.

Not all of these objectives are equally important. For example, Nos. 3, 4, and 5 are not essential but they are highly desirable. The ability to prepare the patient within 24 hours provides flexibility in scheduling operations and avoids the exhausting effect of drawn out procedures. Furthermore, the ability to repeat or to maintain a sterile or near sterile state makes last minute cancellation of surgery acceptable to both surgeon and patient.

Should a housewife be presented with these objectives, she might well suggest a good purge. And this is precisely what surgeons did until, with the coming of the chemotherapeutic era, they fell under the spell of the "wonder drugs." One unfortunate aspect of experimental chemotherapy, however, has been the tendency to give these drugs all the credit for a good result when they actually played a secondary role. And such is the case with preoperative preparation of the bowel. There can be little doubt that good mechanical cleansing is the most significant single step because, by eliminating the great bulk of fecal matter, it removes most of the microorganisms in the bowel. And the more thorough the cleansing is, the more efficiently the antimicrobial drugs can act since the relatively few residual organisms are much less likely to produce highly resistant mutants.

Mechanical cleansing of the bowel is usually carried out with a combination of laxative and enema. The value of low residue diet as an adjunct in this procedure is doubtful. On the basis of our early results, we discontinued it as unimportant. Our choice of laxative for most patients is castor oil, administered as a single 45 cubic centimeter dose between 3 and 5 o'clock on the afternoon preceding surgery. This amount, we believe, is a moderate dose. That better results may be obtained with two 30 or 60 cubic centimeter doses 1 or 2 days apart became evident from the results of studies to be described. Finally, our limited experience with saline laxatives was quite satisfactory, and it is likely that laxatives such as magnesium citrate are just as effective as castor oil. We used saline enemas on the morning of operation until the returns were clear. This step seems to be an essential one.

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We did not realize the primary importance of good mechanical cleansing when we began our studies, but we became aware of it in 1952 when the results of our oxytetracycline studies were analyzed. About one-half of the 31 patients in this series were nonsurgical cases with essentially normal intestines who were given oxytetracycline continuously for 5 to 25 days to determine the over-all effects of this drug on the intestinal flora. Those patients who developed diarrhea had relatively clean large bowels as determined by stool cultures and sigmoidoscopic examination. On the other hand, stool specimens from persons without diarrhea consistently showed higher counts during oxytetracycline administration than they did beforehand (8). From that time on, the subjects in all series were divided into two groups: one received drug only, the other received drug plus the mechanical cleansing procedure.

In order to provide a basis for determining the actual value of the chemotherapeutic drugs for intestinal use, we studied first the bacteriologic effect of the mechanical cleansing procedure by itself. Therefore, we submitted 11 patients to a mechanical cleansing regimen of 2 doses of castor oil, 30 or 60 cubic centimeters each, given 1 or 2 days apart and followed by enemas as outlined earlier. In three-fourths of the patients, the sigmoid colon contained little fecal matter upon sigmoidoscopic examination. One-third of these patients underwent surgery of the large bowel; the others were prepared in the same manner even though they had normal intestinal tracts. Almost no mucosal irritation was seen.

Even though the amount of residual fecal matter in the sigmoid colon was very small, cultures made from it and from stool specimens yielded colony counts in the range of 10^6 to 10^7 per gram of wet feces. Although this figure sounds high, it still represents a drop of 99 to 99.9 per cent in total count. In other words, only 1 organism in 100 to 1,000 remained. Furthermore, in some instances, specific types such as Escherichia coli and streptococci disappeared completely. It must be noted that much of the bacteriologic work was done with residual fecal matter collected at sigmoidoscopy or by purge.

The disappearance of spores proved to be a reliable indicator of the effectiveness of the procedure because in preliminary specimens this bacterial type was consistently present at the level of 10^3 to 10^4 per gram. The adequacy of the preparation could also be predicted by noting the number of stools produced by the laxative. When the number was 3 or more, a good result almost always ensued. With less than 3, the effect varied.

In summary of this study, we make the points that a relatively clean lower bowel was produced in about three-fourths of the patients, that the number of bacteria per gram of fecal matter was reduced by 99 to 99.9 per cent, although the number of survivors was still quite high, and that there was practically no evidence of mucosal irritation. On the other hand, these favorable results were of short duration, lasting from 12 to 18 hours, and there was considerable variation in the interval between administration of laxative and this period of maximum effect. Finally, 3 of the 11 patients did not respond to castor oil.

At this point, we returned to the evaluation of intestinal antiseptics. Our results with oxytetracycline had convinced us that its use for bowel preparation was contraindicated. Not only had we found it to be ineffective for this purpose but, in addition, we were afraid that its widespread use would jeopardize the future usefulness of this lifesaving drug for the treatment of systemic infections by forcing the development of resistant strains. Our fears were justified. Even though oxytetracycline was not employed extensively for preoperative preparation of the bowel, its wide use otherwise resulted in a significant increase in the resistance of some organisms. For example, during the years 1951 to 1953 the administration of oxytetracycline, in the absence of mechanical cleansing, caused the disappearance of Escherichia coli from the stools in 87 per cent of our subjects, whereas in 1954 to 1955, the comparable figure was 13 per cent, meaning that a complete reversal had occurred in just 2 to 4 years (7).

By 1953, we were convinced that the only chemotherapeutic drugs which should be used in preparing the bowel for surgery are those which (1) have limited usefulness in the treatment of parenteral infections so that the development of resistance by microorganisms or of hypersensitivity by the individual is not a serious matter, and (2) are poorly absorbed from the intestine so that a high concentration can remain in the large intestine. One of us was participating at the time in a study (1) on an evaluation of the combination of neomycin and phthalylsulfa-

thiazole as an intestinal antiseptic. In confirmation of Poth's earlier work, neomycin was found to be more effective than other intestinal antiseptics previously available.

Consequently, we undertook an evaluation of neomycin alone and found its antibacterial action very good with the exception of pseudomonas and some anaerobes. After a brief trial with polymyxin B (100 and 200 mgm. daily doses) by itself, we carried on a rather extensive study with the combination of neomycin and polymyxin. The results of using daily doses of 4.5 grams of neomycin and 200 milligrams of polymyxin B were excellent insofar as bacteria are concerned; but they very promptly induced, in 35 of 37 cases, overgrowth of yeastlike organisms (4). Several dosage levels of neomycin were tried. Amounts less than 4.5 grams were not effective enough and 9 grams produced too much irritation.

The results just mentioned were obtained without the use of mechanical cleansing. When this procedure was added, the effect was definitely better but this time the difference was not nearly so great as it had been earlier with oxytetracycline. There were two reasons postulated as to why mechanical cleansing is not crucial to the success of the neomycin regimen. First, it is basically a more effective antibacterial agent; second, it produces a mechanical cleansing effect through its own diarrhea-inducing property.

Despite our success in achieving good bactericidal action, regular overgrowth of yeasts prevented us from reaching our goal of consistently attaining near sterility in the large bowel. The addition of nystatin to the neomycin-polymyxin regimen answered this problem (4, 6). The simultaneous administration of 1,125,000 units a day not only prevented overgrowth but actually eliminated yeastlike organisms if they were present to begin with. When we added mechanical cleansing to the neomycin-polymyxin-nystatin regimen, we obtained sterile or nearly sterile fecal specimens in one-third of the cases, and from more than one-half of the patients stool specimens were obtained with total counts of 10^3 or less. Unfortunately, however, this state of near sterility could be maintained in most instances for only a few hours and represented a total of no more than 1 to 3 stools. Eventually, we learned that the polymyxin could be eliminated from this program without loss in effectiveness (6).

We had succeeded, therefore, in attaining some of our objectives but not all of them. A clean bowel was achieved quite regularly within 24 hours. A sterile or near sterile state could be obtained in about one-half of attempts, although only for a period up to 2 days, and this could be accomplished with a minimum of mucosal irritation. Our attempts to repeat the procedure within a few days were limited, but it seemed likely that this could be done satisfactorily from the bacteriologic viewpoint.

RECOMMENDED PROGRAM FOR PREOPERATIVE PREPARATION OF THE BOWEL

On the basis of this 5 year study, we evolved a procedure which is successful in actual practice. It consists of: neomycin, 4.5 grams, and nystatin, 1,125,000 units, in 3 divided doses at 8 hour intervals beginning at 2:00 p.m. on the day before surgery. At about 3:00 p.m. of that day, 45 cubic centimeters of castor oil are given, and the next morning saline enemas are given until the returns are clear. Inclusion of polymyxin B is optional. In case of serious obstruction, the castor oil is omitted.

We encountered practically no evidence of large bowel irritation. One or 2 of the 53 patients on the lower neomycin regimens (3 or 4.5 gm. per day) complained of epigastric burning which was controlled by giving soda crackers.

The complete absence of enterocolitis was a striking feature of our several neomycin studies which totaled 77 patients. This was true in spite of the fact that several patients on a neomycin (no nystatin) regimen showed large numbers and sometimes pure cultures of Candida albicans in stool cultures. Probably a much better explanation for the absence of enterocolitis in our patients is the remarkable capacity of neomycin for suppressing staphylococci (5). Only 3 patients yielded stool cultures which showed staphylococci during the time neomycin assays were positive.

DISCUSSION AND CONCLUSIONS

The roles of the individual components in the procedure just recommended can be summarized as follows: First, mechanical cleansing by itself greatly reduces the bulk of the fecal mass and correspondingly reduces the number of microorganisms. Unfortunately, however, only one-half of the patients responded satisfactorily, and the effects were very temporary.

Second, neomycin, with or without polymyxin B, tends to produce frequent soft or semiliquid stools and sometimes a frank diarrhea. Thus, this antibiotic provides to some extent its own mechanical cleansing effect. In addition, it is an excellent bacteriocide—certainly the best of those studied by us—and the property of suppressing staphylococci may account for the absence of enterocolitis with the use of this drug. The only drawback of neomycin as an intestinal antiseptic is the rapidity with which it stimulates overgrowth of yeastlike fungi. Third, nystatin rids the bowel of yeasts.

Thus, it is possible with this regimen to attain for a period of 12 to 24 hours a state of near sterility in about one-half of patients who have a patent intestinal lumen or only partial obstruction.

Now that we have put together what we consider to be the best bowel preparation available, there arises the disturbing question, "should we use it?" Superficially, the answer is "yes," for is it not our intent to have the bowel clean and as nearly sterile as possible? However, there are other factors to be considered. The principal one is bacterial resistance. At the present time, the world is infested by an antibiotic resistant staphylococcus which is causing serious infection. Neomycin is perhaps the only truly bacteriocidal agent still effective against this organism and, although it is toxic, we have been forced to use it systemically on occasion and have been thankful for its availability and effectiveness. Thus, the use of neomycin may mean loss of effectiveness through development of bacterial mutation. This can happen; we have seen Escherichia coli and staphylococcus become resistant to oxytetracycline (2, 7). Recently, we have been encountering fecal organisms resistant to neomycin which were not resistant previously. This in itself is an excellent reason to limit the use of neomycin. The same might be said for antibiotics in general. Partial bacterial resistance to these antibacterial agents could produce a bacterial enteritis such as that associated with staphylococcus following the use of oxytetracycline.

On the other hand, what is gained when antibacterial agents are used in bowel preparation? They do materially decrease the fecal flora beyond the point obtainable with mechanical cleansing alone and they prolong the period of low counts, but is this additional effect really needed? Antibacterial agents have been shown to protect a vascular deficient anastomosis but is not vascular deficiency of an anastomosis usually the fault of surgical technique? Antibacterial agents appear to extend recovery from shock, but cannot this be adequately controlled in most cases by proper replacement of fluid and blood?

The question as to whether antibiotics should be used for bowel preparation cannot be answered categorically but must be decided by each physician after he has studied the situation. After more than 5 years of research and much consideration of the subject, we decided to abandon the use of antibacterial agents in the bowel preparation procedure in all cases uncomplicated by significant obstruction, significant arteriosclerotic vascular disease, or anticipated extensive surgery because the advantages do not often enough outweigh the disadvantages.

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MANAGEMENT OF BILE DUCT STRICTURES WITH ASSOCIATED PORTAL HYPERTENSION

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THE DIFFICULTIES which are superimposed upon the already complex problem of bile duct stricture by the development of portal hypertension and hypersplenism are not generally appreciated. It is our purpose to present 12 cases in which this problem was managed by splenectomy (with and without splenorenal shunt) during the past 15 years. A brief résumé of these cases illustrates the chronologic development of our present approach to this problem.

CASE 1. A man, aged 34 years, had undergone cholecystectomy in 1933. End-to-end repair of a common bile duct stricture was performed in 1942. He was seen at the Lahey Clinic in July 1943 at which time common duct exploration and dilatation of persistent stricture were performed. Jaundice was not relieved, and hemolytic anemia developed in association with hepatosplenomegaly. Splenectomy was performed on December 14, and repair of the common bile duct over a vitallium tube was carried out on December 24, 1943. A further end-to-end repair was performed in August 1945 using a long arm T tube. After operation he dislodged the T tube. The common duct was again explored and the tube reinserted in September 1945. The patient has been free of jaundice since 1947, although liver function tests had not returned to normal. He was well when last seen in October 1956. (Eight operations—alive and well 23 years after bile duct injury.)

CASE 2. A 52 year old woman was submitted to cholecystectomy in November 1941. End-to-end bile duct repair was carried out in August 1942. She was seen at the Lahey Clinic in March 1943, when choledochojejunostomy was performed. Revision of the choledochojejunostomy over a vitallium tube was performed in September 1943. The patient remained free of jaundice but returned 10 years later because of thrombocytopenic purpura. The liver was palpable, but the spleen was not. Splenectomy was performed in March 1953. She was well in March 1957. (Five operations—alive and well 16 years after bile duct injury.)

CASE 3. A man, aged 40 years, underwent cholecystectomy in 1948. Common duct repair was performed in 1949. An exploratory operation was performed at the Lahey Clinic early in 1951 because of massive gastrointestinal hemorrhage; the diagnosis of bleeding varices was established and no definitive surgery was performed. The common hepatic duct was drained externally a few months later. Within 6 months, a spontaneous internal biliary fistula developed; this adequately decompressed the biliary obstruction until the patient's death in May 1957. Splenorenal shunt had been established in July 1953 because of recurrent esophageal bleeding. No jaundice or gastrointestinal bleeding appeared thereafter. He died of acute glomerulonephritis in May 1957. The records of an autopsy performed elsewhere give no specific statement as to the patency of the shunt. (Five operations—9 year survival from original bile duct injury to date of death from unrelated causes.)

CASE 4. A woman, aged 34 years, underwent cholecystectomy and common duct exploration in October 1951. Common duct repair was performed in March 1952, and choledochojejunostomy established in November 1952. A right subphrenic abscess was drained 14 months later. When seen at the Lahey Clinic in September 1954 the patient had jaundice and severe hemolytic anemia. It was thought that a shunt would be required, but this was not performed when normal pressures and lack of varicosity were noted at operation. Three weeks after the splenectomy, hepaticojejunostomy was carried out. She was in good health when seen in August 1957. (Six operations—well 6 years after bile duct injury.)

CASE 5. A 30 year old woman had had a cholecystectomy in 1952. She was seen at the clinic in April 1955 because of bleeding esophageal varices and jaundice. A splenorenal shunt was performed May 5, 1955. External drainage of the common hepatic duct was established in August 1955. Choledochojejunostomy was carried out 3 weeks later, and liver biopsy at this time revealed primary hepatoma. The patient died in January 1956 of massive gastrointestinal hemorrhage. (Four operations—dead of complications of bile duct injury after 4 years.)

CASE 6. A 40 year old woman underwent cholecystectomy in 1950. Common duct repair was performed in 1951. A second attempt at common duct repair was made in 1953. She was seen at the Lahey Clinic in March 1955 because of bleeding varices, splenomegaly, and edema secondary to mitral stenosis. External drainage of the common hepatic duct was established in April 1955, and splenorenal shunt in May 1955; hepaticoduodenostomy was performed in June 1955. Duodenojejunostomy for relief of duodenal obstruction was carried out 3 weeks later. Closure of a duodenal fistula was performed in July 1955. The patient died several weeks later from liver failure and the effects of the duodenal fistula. (Eight operations—died from complications of surgery to correct bile duct injury received 5 years previously.)

CASE 7. A woman, aged 61 years, underwent cholecystectomy in 1948, at which time a common

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TABLE I.—MANAGEMENT OF STRICTURES OF THE BILE DUCT WITH ASSOCIATED PORTAL HYPERTENSION

Case No.	Operative procedure	Indications	Postoperative course	Technical appraisal of shunt at operation	Clinical appraisal of shunt after operation	Liver function after operation (last visit)	Date of operative procedure	Comment
1	Abdominal splenectomy	Hemolytic anemia	Uneventful			Improved	1943	Alive 23 years after bile duct injury
2	Abdominal splenectomy	Thrombocytopenic purpura	Subphrenic abscess			No change	1953	Alive 16 years after bile duct injury
3	Transabdominal splenorenal shunt	Bleeding varices	Uneventful	Adequate	Patent	No change	1953	Died 1957, acute glomerulonephritis; no gastrointestinal bleeding
4	Abdominal splenectomy	Hemolytic anemia	Subphrenic abscess			Improved	1954	No preoperative or postoperative evidence of portal hypertension through 1957
5	Thoracoabdominal splenorenal shunt	Bleeding varices	Hematemesis 14th day	Excellent	Thrombosed	Worse	1955	Died of gastrointestinal hemorrhage 8 months after operation; primary carcinoma in liver biopsy
6	Thoracoabdominal splenorenal shunt	Bleeding varices	Uneventful (died after biliary reconstruction)	Excellent	Patent	No change	1955	Splenorenal shunt procedure uneventful; died after biliary reconstruction
7	Thoracoabdominal splenorenal shunt	Hypersplenism; varices without bleeding	Uneventful	Adequate	Patent	No data	1957	Died of myocardial infarct; shunt patent at autopsy
8	Thoracoabdominal splenorenal shunt	Bleeding varices	Subphrenic abscess; atelectasis; pneumonitis	Adequate	Patent	No data	1957	Bled 8 months after operation; alive 9 years after bile duct injury
9	Thoracoabdominal splenorenal shunt	Bleeding varices; hypersplenism	Hematemesis 12th day	Unsatisfactory	Thrombosed	No data	1957	Operative injury to renal vein; died 10 months after operation
10	Thoracoabdominal splenectomy	Hypersplenism; varices without bleeding	Uneventful			Improved	1957	General health greatly improved
11	Thoracoabdominal splenorenal shunt	Bleeding varices; hypersplenism	Uneventful	Excellent	Patent	Worse	1957	Prognosis poor despite excellent surgical decompression
12	Thoracoabdominal splenorenal shunt	Bleeding varices; hypersplenism	Evisceration; omental hemorrhage; liver failure	Unsatisfactory	Thrombosed	Worse	1957	Operative mortality

duct injury was recognized and repaired primarily. A second end-to-repair was carried out in 1949. She came to the Lahey Clinic in 1957 for treatment of severe hypersplenism and varices which had not yet bled. Splenorenal shunt was established in March 1957. The patient died of a myocardial infarction in October 1957. At autopsy the shunt was widely patent. (Three operations—9 year survival from date of original ductal injury to death from unrelated causes.)

CASE 8. A 36 year old woman was submitted to cholecystectomy in 1948. Six months later transduodenal sphincterotomy was performed. End-to-end repair of the common duct was carried out later in the same year. She came to the clinic in 1956; hepaticojejunostomy over a Y tube was performed in May, and a subphrenic abscess drained in June. Splenorenal shunt for bleeding varices was established in March 1957. The Y tube was removed through the jejunum in May 1957. The patient had an episode of melena from gastric varices in November 1957, but jaundice has not recurred. (Seven operations—alive 9 years after original bile duct injury.)

CASE 9. A woman, aged 50 years, underwent cholecystectomy in 1950. Common duct repair was performed in 1951. She was seen at the Lahey Clinic in 1953, at which time external drainage of the common hepatic duct was established. End-to-end repair of the duct was carried out in 1954. Drainage was prolonged and a spontaneous internal fistula subsequently developed. When she returned 2 years later, bleeding esophageal varices and hypersplenism were present. A splenorenal shunt was established in May 1957. The patient died in March 1958. (Five operations—dead of complications 8 years after original injury.)

CASE 10. A 43 year old woman underwent cholecystectomy in 1942. Bilateral tubal ligation was carried out in 1945. An exploratory operation on the common bile duct in 1946 was complicated by cardiac arrest which required thoracotomy, and evisceration 2 weeks after operation necessitated emergency resuture of the abdominal incision. The common duct was again explored in 1952. Pinning of the hip was carried out at the Lahey Clinic in 1956 for a femoral neck fracture incurred during an epileptic seizure. Drainage of the left hepatic duct with removal of several stones was accomplished in October 1956, at which time severe atrophy of the right lobe of the liver was noted. Early in 1957 a spontaneous internal fistula developed. Severe hypersplenism and esophageal varices which had not bled were treated by thoracoabdominal splenectomy in June 1957. The splenic vein was too short to reach a medially displaced kidney and no shunt was established. The Smith-Petersen nail was removed from the patient's hip in October 1957, at which time her general health was remarkably good. (Six operations related to biliary tract—alive and well 15 years after original injury.)

CASE 11. A 41 year old woman was submitted to cholecystectomy in March 1953. An exploratory operation on the common duct was performed in July 1953, and again in December of that year. An intrahepatic cholangiojejunostomy was attempted in November 1954. When seen at the Lahey Clinic in 1957 she had severe hypersplenism, bleeding esophageal varices, and intense jaundice of 4 years' duration. External drainage of the common hepatic duct was established in August 1957. A splenorenal shunt was performed in September 1957; this stopped the bleeding and hemolysis. A cholangiogram through the drainage tube outlined all radicles of the intrahepatic biliary tree. However, 4 years of unrelieved jaundice had damaged the liver so badly that we have little hope for any significant return of function. The patient was still alive in January 1958. (Six operations—alive 4 years after original injury.)

CASE 12. A man, aged 41 years, underwent cholecystectomy in 1944; a common duct injury was recognized and was repaired over a Y tube. The common duct was explored and the Y tube removed in 1949. He came to the Lahey Clinic in 1957 because of mild jaundice and bleeding esophageal varices. A splenorenal shunt was established in September 1957. The patient died 2 weeks after operation, of liver failure caused dy evisceration and massive hemorrhage from the omentum. (Three operations—dead 13 years after original injury, from complications of surgery to relieve portal hypertension.)

DISCUSSION

The complexity of the problems encountered is apparent from a careful perusal of the preceding case histories. The effectiveness of shunt procedures, the status of liver function postoperatively, and the morbidity associated with these procedures are outlined in Table I.

Approximately 800 operations for bile duct stricture have been performed at the Lahey Clinic through the year 1957. Many of these patients show significant evidence of portal hypertension or hypersplenism, or both. However, only 12 patients have required splenectomy (8 with an associated shunt) to control this facet of biliary cirrhosis caused by bile duct stricture.

We have gradually evolved a plan of management in these severe cases of portal hypertension. If a high grade of biliary obstruction is present, particularly if it is of long duration and if it is technically difficult to repair, external drainage of the common hepatic duct alone is employed as a first stage procedure. Three to 4 weeks later, if the liver function shows signs of progressive improvement, splenorenal shunt is established. These patients need frequent transfusions because of hemolysis and insidiously bleeding varices; for this reason we prefer to establish a splenorenal shunt as soon after external biliary decompression as the return of adequate liver function will permit. Definitive reconstruction of the bile ducts can be carried out at any time thereafter, when liver function is at an optimum level.

In patients demonstrating lesser degrees of bile duct obstruction and in whom the major problem is hypersplenism or massive esophageal bleeding (which occasionally cannot be controlled with balloon tamponade), a splenorenal shunt is established as a first stage procedure. Definitive biliary reconstruction can usually be accomplished in one additional operation.

We prefer to utilize the splenorenal shunt exclusively in these patients, as most of them have some degree of active hepatitis and whether or not complete diversion of portal venous blood (portacaval shunt) will aggravate liver function in such patients is not known. A portacaval shunt was established in 1 of our patients who had sclerosing choledochitis; the result was excellent decompression of the esophageal varices. The establishment of a portacaval shunt is technically possible in patients with recurrent bile duct stricture, but the likelihood that further reconstructive work will be required on the bile ducts is so great that the anastomosis will be in jeopardy at that time and also will contribute to technical difficulties when biliary reconstruction is attempted. Furthermore, hypersplenism was the major or secondary problem in 5 of the 8 patients who underwent a shunt procedure. A shunt procedure was not performed in 1 case because of technical difficulties; the major indication was hypersplenism and fortunately this patient has not bled to date.

It must be emphasized that portal hypertension is a common accompaniment of biliary strictures when adequate decompression or reconstruction has not been accomplished. If the obstruction to the flow of bile is permanently relieved, even in the presence of considerable portal hypertension most patients will have no further trouble from hypersplenism or bleeding varices.

SUMMARY

Twelve cases of bile duct stricture have been reported. These patients have undergone splenectomy or the establishment of a splenorenal shunt for bleeding varices, hypersplenism, or both. One operative death occurred in this group of patients, and as a group they may be regarded as some of the worst surgical risks ever likely to be encountered.

Four of 8 splenorenal shunts are patent from 6 months to 3 years after operation. Bleeding occurred 8 months after the shunt procedure in 1 patient. Roentgenologic studies in this case revealed a fundal lesion, probably representing gastric varices. This patient had a subphrenic abscess which required drainage. It is quite likely that even an excellent anastomosis will thrombose in the presence of a subphrenic abscess, and if further esophageal bleeding occurs under these circumstances, portacaval shunt or limited esophagogastrectomy should probably be considered (provided biliary decompression has remained adequate).

In 2 cases, the anastomoses were technically unsatisfactory; operative injury to the renal vein and inadequate size of the splenic vein were the factors involved. These 2 patients died of hemorrhage 10 months and 2 weeks postoperatively.

In the final case, the shunt was technically excellent but hematemesis was demonstrated on the fourteenth postoperative day. This patient died of upper gastrointestinal hemorrhage 8 months later. The presence of primary carcinoma of the liver superimposed on biliary cirrhosis had been established by biopsy at the time that the choledochojejunostomy was performed.

Splenectomy alone was carried out in 4 cases and these patients are alive without evidence of gastrointestinal bleeding 1, 3, 4, and 13 years after splenectomy. Varices which had never bled were present preoperatively in 1 of these cases. Further bile duct reconstruction has not been required in any of these patients, which is the major reason why they have done so well.

Suggestions for managing this fascinating and complex problem have been outlined.

VALUE OF HYPOTHERMIA AND ARTERIAL OCCLUSION IN THE TREATMENT OF INTRACRANIAL ANEURYSMS

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THE APPROPRIATE TREATMENT of patients with intracranial aneurysms remains uncertain. Some type of surgical approach is generally accepted as necessary, however, in view of the high mortality associated with rupture of the lesion. The ideal surgical treatment achieves exclusion of the aneurysm from the intracranial circulation without compromising the blood supply to the brain. This may be accomplished by either ligating or clipping the neck of the aneurysm or by "trapping" it between clips or ligatures placed on the parent vessel if collateral circulation can be maintained.

Proximal ligation of either the common or internal carotid artery in the neck is an alternative method of treatment. The objective here is to decrease the pressure and pulsation within the aneurysm in order to reduce its size, allow thickening of the wall, and promote the formation of a protective clot within the lumen. Although proof of the ultimate value of proximal carotid ligation in preventing later hemorrhage from intracranial aneurysms awaits long term follow-up observations on patients who have been treated by this technique, the recently published series of cases reported by Black and Davis and their associates are nevertheless encouraging.

We have seen 2 instances in which recurrent subarachnoid hemorrhage occurred as late as 8 and 10 years following carotid ligation. In the series reported by Davis and co-workers of 75 patients who were operated upon, 14 died in the immediate postoperative period and 5 died of progression of their disease following discharge from the hospital. We have also had the disturbing experience of having fatal hemorrhage occur within a few days after proximal carotid ligation. It is our opinion, therefore, that analogous to the management of aneurysms elsewhere in the arterial tree, local repair of intracranial aneurysms is desirable when it is feasible.

Until recently, however, clipping the neck of a large aneurysm, particularly one which arises from a bifurcation of a vessel, has carried a high operative risk. Poppen states: "The excision of aneurysms also is attended with a reasonably low mortality if aneurysms that arise from the bifurcations are not included. For that reason I strongly recommend great caution before decision is made to attack an aneurysm that arises from a bifurcation unless a suitable neck for the application of a silver clip can be demonstrated."

Hypothermia, with temporary occlusion of part or the entire intracranial arterial inflow, has facilitated the direct surgical attack on intracranial aneurysms. Botterell and co-workers (3) have pointed out the advantages of this technique which, because of the decrease in cerebral metabolism, allows a longer period of partial or complete interruption of the circulation than was formerly possible.

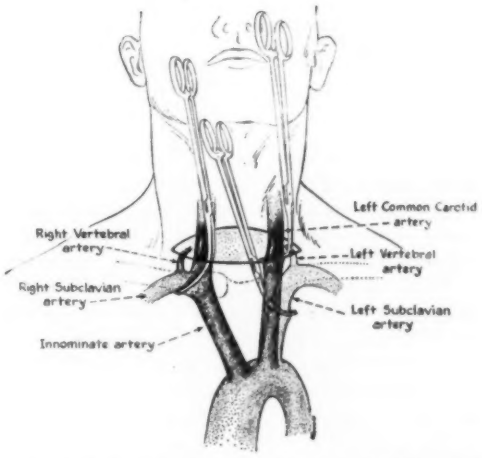

FIG. 1. Drawing to illustrate position of arterial clamps for total cerebral arterial inflow occlusion.

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TABLE I.—SUMMARY OF FIRST 6 CASES

Case No. Age of patient, yrs.	*Location of aneurysm Diameter of neck, cm.*	*Interval between hemorrhage and operation*	*Preoperative status*	*Body temp. at occlusion Length of occlusion*	*Complications Length of follow-up*	*Results and comments*
1 25	Anter. communicating artery (Fig. 2a) 1.5	6 mos.	No symptoms	28.2° C. 4′ 25″	Pneumothorax 15 mos.	Comp. recovery. Progress arteriography 4 mos. postop. failed to show lesion (Fig. 2b)
2 52	Right middle cerebral artery (Fig. 3a) 2.0	10 days	Disoriented. Papilledema. Systemic blood pressure 210/110	27.0° C. 8′	None 14 mos.	Gradual clinical recovery. Progress arteriography 5 mos. postop. failed to show lesion (Fig. 3b). Results of clinical exam. at this time were normal
3 39	Right ant. cerebral, anterior communicating complex (Fig. 4) Not measured	2 episodes of hemorrhage, 2 mos. and 1 mo. preop.	Comp. amnesia for preceding 6 weeks	28.0° C. None	Cardiac arrest, 12 mins. 14 mos.	Aneurysm filled only from right side preop. Progress arteriography 6 mos. postop. showed lesion now filled from left (Figs. 5 and 6). Asymptomatic when last seen
4 53	Left ant. cerebral, ant. communicating complex (Fig. 7) 2.0	2 episodes of hemorrhage, 10 yrs. and 1 mo. preop.	Essential hypertension (BP 190/110). Hyperactive reflexes on right	28.5° C. 6′	None 15 mos.	Neither ant. cerebral art. filled from injection of right carotid artery. Injection of left carotid artery filled the aneurysm and both ant. cerebral arteries. Progress arteriography 3 mos. postop. did not reveal filling of lesion (Fig. 7b). Asymptomatic at this time
5 54	Bifurcation of right internal carotid artery 1.7	3 episodes of hemorrhage, 10 yrs., 3 days, and 24 hrs. preop.	Clouded sensorium. Compl. palsy of right third nerve. Papilledema	27.3° C. 8′ 30″	Cardiac arrest, 26 mins. 7 mos.	Disappearance of third nerve palsy. Asymptomatic when last seen. Progress arteriography has not yet been done
6 38	Right internal carotid, posterior communicating artery 1.0	1 mo.	Partial palsy of third nerve. Intermittently disoriented. Papilledema. Hypertension (BP 190/100)	28.0° C. 10′	Compl. palsy of right third nerve 4 mos.	Compl. recovery with exception of third nerve palsy. Progress arteriography has not yet been done

Other advantages are an induced compensated hypotension and a corresponding decrease in cerebral blood flow, as well as reduction in brain volume and cerebrospinal fluid pressure which aid retraction of the brain and exposure.

We have been attracted to the feasibility of total arterial inflow occlusion just prior to intracranial aneurysmorrhaphy. This technique reduces the size of the aneurysm, avoids rupture, and makes possible treatment of large lesions previously regarded as inoperable. In their most recent publication, Botterell and co-workers (2) state that in their later cases the common carotid arteries (but apparently not the vertebrals) have been occluded immediately before application of a clip or ligature to the aneurysm.

Twelve cases are reported in which a direct surgical approach to the repair of intracranial aneurysms was aided by the application of these methods (Table I).

Hypothermia to levels of from 27 to 30 degrees C. was obtained by preliminary immersion of the patient in an ice tub and subsequent transfer to a Therm-o-Rite blanket. The intracranial aneurysm and the superior mediastinal arteries were exposed simultaneously by 2 surgical teams. During the dissection of the aneurysm, systemic arterial hypotension was induced by

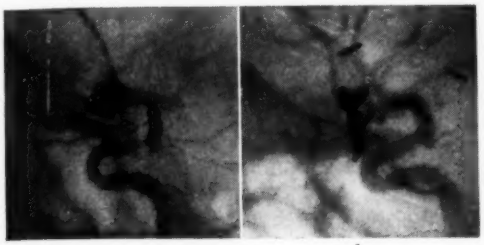

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FIG. 2.

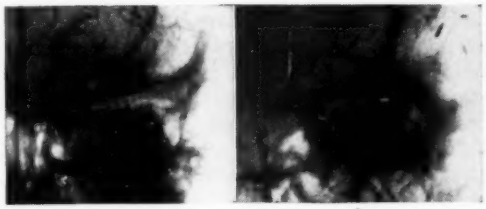

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FIG. 3.

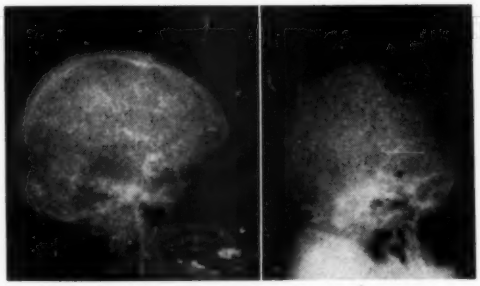

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FIG. 4.

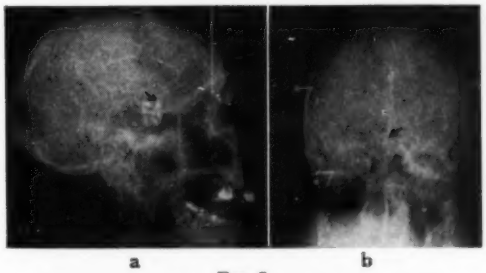

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FIG. 5.

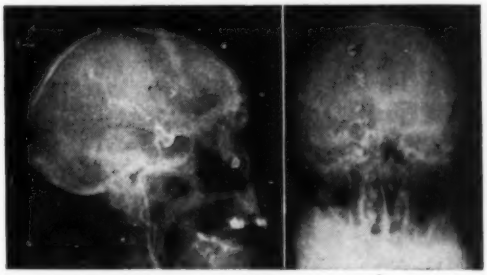

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FIG. 6.

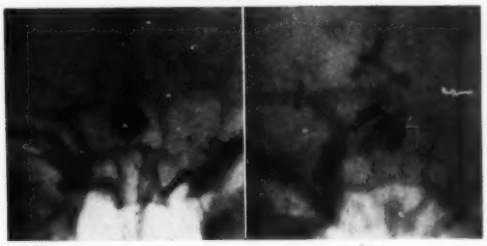

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FIG. 7.

FIG. 2. Case 1. Arteriograms of aneurysm of anterior communicating artery, oblique view. a, Preoperative. Note spasm of internal carotid and distal branches. b, Postoperative.

FIG. 3. Case 2. Arteriograms of aneurysm of right middle cerebral artery, anteroposterior view. a, Preoperative. Note extreme spasm of internal carotid artery and particularly of the middle cerebral artery, indicated by arrow. b, Postoperative. Arrow points to the normal appearance of the middle cerebral artery.

FIG. 4. Case 3. Preoperative arteriograms of aneurysm of right anterior-cerebral, anterior-communicating complex. a, Lateral view. b, Oblique view. Note the large daughter aneurysm, indicated by an arrow.

FIG. 5. Case 3. Postoperative arteriograms of left carotid artery. a, Anteroposterior, and, b, lateral views. Note aneurysm.

FIG. 6. Case 3. Postoperative views of right carotid artery. a, Lateral, and, b, anteroposterior views. Note lack of filling of aneurysm and occlusion of anterior cerebral artery.

FIG. 7. Case 4. Arteriograms of left carotid artery, anteroposterior view, showing aneurysm of left anterior-cerebral, anterior-communicating complex. a, Preoperative. b, Postoperative. Note spasm of carotid artery and its branches.

arfonad.[1] We believe that the danger of rupture is reduced by this means. However, caution must be exercised since in our experience the hypothermic state sensitizes the cardiovascular system to hypotensive agents of this nature, although others have not found this to be true.

[1]Arfonad (d-3,4 (1′,3′-dibenzyl-2′-keto-imidazolido)-1,2-trimethylene thiophanium d-camphorsulfonate).

Access to the afferent arteries is obtained through a cervical approach to the superior mediastinum. Due to the frequent friability of the vertebral arteries, we believe it advisable to reduce flow within them by applying clamps to the major arteries proximal to the origins of the vertebral arteries. On the right side this is accomplished by clamping the innominate artery at its point of bifurcation, thereby interrupting the flow in the common carotid as well. The innominate artery is exposed most easily through a plane developed medial to the sternohyoid and sternothyroid muscles. On the left side the common carotid artery is exposed through a plane lateral to the strap muscles. The left vertebral artery branches from the left subclavian artery just above the level of the clavicle.

Contrary to the lateral position it is shown to have in most anatomic illustrations, the subclavian artery, as it leaves the superior mediastinum, lies posterior to the common carotid artery and 3 centimeters beneath it. Exposure adequate for clamping the subclavian artery proximal to the origin of the vertebral artery can be obtained by a deeper and slightly caudad development of the exposure obtained for clamping the left common carotid artery. The arterial segments to be occluded are loosely encircled with rubber tubing, with which they may be brought forward for later clamping. The position of the occluding clamps is illustrated in Figure 1.

Repair of the aneurysm was effected by neck occlusion with 1 or, if necessary, 2 Olivecrona clips in 4 cases, by suture occlusion in 1 case, and by proximal arterial ligation in 1 case. Following repair of the aneurysm, the mediastinal arteries were reopened. Total occlusion periods varied from 4 to 10 minutes.

The complications encountered were largely avoidable. Temporary cardiac arrest occurred in 2 patients (Cases 3 and 5); in 1 of these patients, cardiac arrest was due to an overdose of arfonad and in the other patient to uncompensated blood loss which produced an abrupt and severe drop in arterial blood pressure. Manual massage restored cardiac function in both patients and no organ damage resulted.

During a follow-up period of from 4 to 15 months, 6 patients have remained well. Six other patients have been operated upon too recently to be of significance in a follow-up study. Postoperative arteriograms were taken in 4 cases. These studies showed normal arterial contour of the intracranial vessels in 3 cases. In 1 patient (Case 3) in whom proximal arterial ligation was performed in preference to aneurysmorrhaphy, postoperative arteriograms demonstrated filling of the aneurysm from the opposite side (Fig. 5). In this patient cardiac arrest developed during exposure of the aneurysm and since the lesion filled only in the right carotid arteriogram (Fig. 4) it was decided to terminate the procedure as rapidly as possible by clipping the right anterior cerebral artery. In retrospect it would have been a simple matter to have completed the dissection and to have clipped the base of the aneurysm, since it was completely collapsed during the period of arrest. One patient died from recurrent hemorrhage.

The advantages of this surgical technique are those previously commented upon of hypothermia itself, plus the ability to occlude a large aneurysm safely without tearing it or a parent vessel during the process. The flaccid aneurysmal wall could be safely grasped and its neck obliterated unhurriedly under direct vision with preservation of a normal lumen in the parent artery. It is probable, therefore, that the combination of hypothermia and total arterial inflow occlusion will render many lesions readily operable which might otherwise be considered inoperable because of their size and location.

It is interesting to note that even with total occlusion of the left common carotid, subclavian, and right innominate arteries some blood may reach the cranium. In some patients who were operated upon before the present series and in whom bleeding from the aneurysm occurred, hemorrhage was greatly reduced, but not completely controlled, by occlusion of the neck vessels. This has been commented upon by Welch. Thus, once bleeding has occurred it may be necessary to clip an important vessel. It is for these reasons that we wish to emphasize the value of performing total arterial inflow occlusion prior to attacking the aneurysm, rather than waiting for hemorrhage to occur.

SUMMARY

Twelve patients are reported upon in whom a direct surgical attack on large intracranial aneurysms arising at a bifurcation of a vessel was made, utilizing hypothermia and total arterial inflow occlusion prior to the application of the occluding clip or ligature to the base of the

aneurysm. There was 1 operative death due to recurrent hemorrhage.

Emphasis has been given to the need for avoiding rupture during dissection of the aneurysm and during the application of a clip to the base of the aneurysm by prior inflow occlusion.

It is believed that many lesions previously considered inoperable may be made safely operable by this technique.

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Reviews of New Books

THE THIRD NUMBER of the quarterly series entitled *Clinical Obstetrics and Gynecology*[1] is comprised of two symposia; one deals with special diagnostic aids and the other with abnormal uterine bleeding. Both are ably edited and the list of contributors is impressive. The diagnostic aids that have been compiled reflect generally the more recent trends in this field in both obstetrics and gynecology. In all instances, the material is presented concisely with adequate descriptions of the role that each could play in helping one to reach a clinical diagnosis. There are excellent illustrations and descriptions of the techniques of each test.

The section on abnormal uterine bleeding touches on practically all of the entities which give rise to this symptom. The specific abnormalities are well defined, and those which are most commonly found in practice are given justifiably more comment. Most of the emphasis is placed upon the importance of symptoms and accurate diagnosis. However, there is detail enough in treatment so that the reader is left with a mode of management of most of these problems.

Throughout the book there is a certain amount of repetition. This, however, does not detract materially from the work. It serves to emphasize certain features (e.g., cytologic examination) but more important, it gives the reader a brief glimpse of the differences of opinion of some of the authors. This should serve to stimulate the reader to further investigation of any particular problem which interests him.

—*Leon A. Carrow.*

SEVEN CONTRIBUTORS and Robert S. Pollack have presented a brief compilation of current clinical knowledge concerning the treatment of benign and malignant breast tumors. The book entitled *Treatment of Breast Tumors*[2] is relatively short containing only 147 pages with 47 plates and 16 figures.

The author has arranged the book into two main parts. The first part contains a pathologic classification of breast tumors, benign breast tumors, gynecomastia, and infections of the breast. The second part concerns many of the problems encountered in the treatment of primary and advanced breast cancer.

In the first section of the book, the author has allowed 3 pages to be devoted to the rather doubtful value of the medical treatment of chronic cystic mastitis, whereas fibroadenomas are discussed in only 1 page.

In the second section of the book, the author devotes a chapter to "Extended Radical Mastectomy" but he has accorded only 3 paragraphs to the technique of radical mastectomy which he considers the "preferred method of treating breast cancer."

The illustrations are particularly well done and the chapter on radiotherapy is excellent. Plate 35-A referred to in the text is probably the insert of Plate 35 but this component is not so designated.

The general practitioner and medical student should find this book informative and concise although the experienced surgeon would find it somewhat sketchy and perhaps elementary.

—*Edward F. Lewison.*

THE AUTHOR of *Difficult Diagnosis*[3] has not intended to set forth this book as a "primer" in differential diagnostics nor as a textbook on rare diseases. He has rather set its orientation on an advanced postgraduate level for clinicians who may wish to be able to refer to systematized groupings of related conditions that are most apt to produce obscure illness. The accent is, therefore, not on the classic syndromes of disease entities, but rather on the earlier, atypical or forme fruste manifestations of these conditions.

The book is divided into two sections. The first part entitled Groupings of Related Diseases Frequently Producing Puzzling Illness is presented in 17 chapters starting with the endocrinopathies. A chapter devoted to cutaneous medicine stresses "dermatopathology as the window to systemic medicine," and emphasizes the physiologic interrelationship between the skin and the nervous, circulatory, and endocrinal systems. Ninety-nine helpful illustrations are included. Another chapter on obscure postoperative complications systematically organizes for ready reference the possible entities to be considered when one is faced with such a situation. The pitfalls of an overly aggressive approach to the diagnostic interpretation of laboratory and radio-

[1]CLINICAL OBSTETRICS AND GYNECOLOGY. Vol. I. No. 3. Symposium on Special Diagnostic Aids. Edited by C. Paul Hodgkinson, M.D., and Symposium on Abnormal Uterine Bleeding. Edited by John I. Brewer, M.D. 852 pages, illustrated. New York: Paul B. Hoeber, Inc., 1958.

[2]TREATMENT OF BREAST TUMORS. By Robert S. Pollack, M.D., F.A.C.S. 147 pages, 53 illustrations. $6.00. Philadelphia: Lea & Febiger, 1958.

[3]DIFFICULT DIAGNOSIS; A GUIDE TO THE INTERPRETATION OF OBSCURE ILLNESS. By H. J. Roberts, M.D. 913 pages, 99 illustrations. Philadelphia and London: W. B. Saunders Co., 1958.

graphic findings and the illnesses produced by drug therapy are presented and discussed in the chapter "Iatrogenic Illness."

The second part of the book entitled A Classification and Analysis of Useful Diagnostic Procedures is devoted to the listings, classification, and concise analysis of the numerous laboratory and clinical diagnostic tests and procedures which are available to most clinicians. Most important and informative are the pertinent remarks following each test which are relative to the importance of that particular procedure. Factors influencing the test are stated as "clinical clues" or "technical notes." A bibliography of over 1,800 references makes it possible to refer to the original authoritative publication if desired.

This is a very scholarly and ably written book. It should serve as an excellent reference for the clinician's orientation in clinical consultation and for discussion in clinicopathologic conferences. It should also be of advantage as a basis for commencing preparation in the examinations on diagnosis given by the various specialty boards. —*Edmund A. Gorvett.*

THE BOOK entitled *Intestinal Obstruction*[4] is concise but is written pleasantly enough that it is good reading despite the fact that it covers a wide range of material.

In the preface, the author states that he strives to present three subjects. The first deals with the salient facts about intestinal obstruction (this concerns almost exclusively the small bowel), and these are presented concisely and without attempting to cover the entire background of the physiologic pathology of obstruction. The second deals with methods of management and the dangers of following them too blindly. While the author has clearcut, definite concepts about treatment, he presents others with fairness, if not too extensively. The third objective is to present a source for further facts, i.e., a bibliography. In this regard he does not offer so selective material as in relation to his first two objectives.

No attempt is made to separate the problems of large and small bowel obstruction, these being discussed alternately, but it is not difficult to determine with which the text deals.

The book is well illustrated with plain, easily understood line drawings; operative procedures concerned with obstruction are presented clearly in this fashion.

The chapter on chronic intestinal obstruction and that on recurrent intestinal obstruction are not so clear and leaves much to be desired. Acute obstruction, recurrent or otherwise, results primarily in physiologic changes, and if treated promptly leaves no stigma which can be seen in the bowel wall. In chronic obstruction there are changes in pathologic anatomy which are not transient. With the exception of Chapter 20, the book presents the story of intestinal obstruction well, even though there are, here and there, individual opinions with which this reviewer disagrees. The subject is presented in good readable form and ought to be useful as a short, concise, yet adequate presentation of an important clinical problem.

[4]INTESTINAL OBSTRUCTION. By Claude E. Welch, M.D., D.Sci.(Hon.). Illustrated by Muriel McLatchie Miller. 376 pages. $10.50. Chicago: The Year Book Publishers, Inc., 1958.

—*Charles G. Johnston.*

VOLUME I of a series of monographs on neoplastic diseases at various sites[5] is edited by J. R. Bignall. Volume II concerns tumors of the bladder and Volume III, cancer of the rectum. Three other volumes dealing with cancer of the prostate, intracranial and spinal tumors, and tumors of the esophagus are in preparation. Other volumes are planned to follow and have as subject matter leukemias, malignant lymphomas, and neoplasms of the larynx, pharynx, thyroid, breast, and uterus.

Bignall is Assistant Physician and Senior Lecturer at the Brompton Hospital and is Research Assistant, Radiotherapy Department, Institute of Cancer Research, Royal Cancer Hospital, London.

Seven others, mostly associates of Bignall's at the Brompton Hospital and the Royal Cancer Hospital, have collaborated in the writing of the chapters concerned with statistics, pathology, surgery, and radiotherapy of cancer of the lung.

The controversial subject of the relation of tobacco smoke and air pollution to the etiology of carcinoma of the lung is presented in an unbiased and scientific manner. The conclusion that cigarette smoking should be regarded as one of the causes of lung cancer is supported by: (1) the observation that histologic changes which commonly precede the development of lung cancer are also related to smoking, (2) the discovery of several carcinogenic substances in tobacco smoke, including one which is believed to be effective in man, and (3) the demonstration that extracts of tobacco tar can, under suitable conditions, cause cancer of the skin in animals.

Statistical studies linking tobacco with the production of lung cancer are of two types: prospective and retrospective. Most studies have been of the retrospective type in which the smoking habits of individuals with and without lung cancer are compared. More significant are the prospective studies in which the mortality in a group of persons whose smoking habits had previously been defined are compared over a period of years. Two reports of the retrospective type, the Hammond and Horn report (the United States, 1954, 1958) and the Doll and Hill report (Great Britain, 1954, 1956) are discussed and compared. Studies of both types incriminate tobacco smoke as an important cause of lung cancer.

More recently, air pollution as a causative factor of carcinoma of the lung has attracted attention. There is a greater incidence of the disease in urban than in rural communities and in urban communities with air pollution than in those without. However, the relative importance of air pollution in this respect is presently not precisely defined.

The first one-third of the text is concerned with studies of mortality from lung cancer and its causation. The remainder of the book deals with the pathology, course of the disease, treatment, and prognosis.

The authors' material is based on a series of 1,749 cases seen at the Brompton Hospital and the Royal

[5]NEOPLASTIC DISEASE AT VARIOUS SITES. General Editor, D. W. Smithers, M.D., F.R.C.P., F.F.R. CARCINOMA OF THE LUNG. Edited by J. R. Bignall, M.D., M.R.C.P. Vol. I. 298 pages, 62 illustrations. $10.50. Edinburgh and London: E. & S. Livingstone Ltd.; Baltimore: Williams & Wilkins Co., 1958.

Marsden Hospital. This series is compared to other large series of patients with lung cancer previously reported in the literature. The authors have indicated the points of similarity and dissimilarity between their patients and those of other authors, thus enabling the reader to consider the subject matter in broad perspective. This is an advantage which is sometimes lacking in American texts.

Three hundred and forty-three patients of this series are available for determination of the 5 year survival rate. The low salvage rate (6 per cent) emphasizes the seriousness of this disease and makes apparent the need for a monograph such as the one prepared by Bignall to present the subject in detail to aid the student and practitioner. This is a valuable reference book on an important subject.

—Frederick W. Preston.

THE FIRST INTERNATIONAL COLLOQUIUM on epilepsy was held in Marseilles, France, in 1954, and the reports of that meeting were later published. In March 1957, the second such colloquium was held in Bethesda, Maryland, and the 56 contributors from 6 different countries constitute a roster of well known names in the fields of both investigative and clinical endeavor in the problem of epilepsy. Though the book, *Temporal Lobe Epilepsy*,[6] reveals the sometimes sharp disagreements which occurred in the meeting over numerous concepts concerning this subject, from an interpretation of the electroencephelograms to the indications for surgical therapy, yet this colloquium—"a give and take affair"—was highly disciplined and productive of much fresh, well co-ordinated information. At no time, apparently, was there a common agreement upon a proper, all inclusive name for the syndrome: psychomotor epilepsy, autonomic, temporal lobe, rhinencephalic, etc.; none of these alone is adequate.

In the multifaceted techniques to be used in the study and treatment of temporal lobe epilepsy, all the resources of electroencephalography, depth electrography, radiology, stereotactic technique, biochemistry, neuropathology, surgical extirpation in both animal and human subjects, and detailed social studies are called upon. The role which these techniques are currently playing in the modern approach to temporal lobe epilepsy is thoroughly illuminated in this unusual book. Of particular, one might say *prophetic*, meaning is the importance which biochemistry is increasingly found to play in this and other elusive disturbances of the brain, and for this reason the chapter "The Evidence for a Neurochemical Basis of Seizures," by Donald B. Tower seems to this reviewer to be the high point of the book.

The surgical attack upon the temporal lobe has not yet become "standardized"; indeed, it probably never shall be. At present, varying amounts of the anterior temporal pole are being removed, as well as the hippocampal gyrus and the amygdala, alone, in combinations, unilaterally, and bilaterally. Results are satisfying in from 35 to 50 per cent of the patients treated, so far as improvement of the seizures is concerned; but it is clear that such extirpation is by no means a measure for improvement of the psychic state.

The book is written in English except for the chapter by J. E. Paillas which is given in French. Through an error, the remarks of Horace W. Magoun are presented twice. The book is well illustrated, and it contains extensive references to the pertinent literature, a contributor's index, and a detailed subject index.

—John Martin.

THE SYMPOSIUM which the book *Breast Cancer*[7] represents was organized as the Second Biennial Louisiana Cancer Conference under the chairmanship of Albert Segaloff. It was held in New Orleans on January 22 and 23, 1958, and sponsored by the Louisiana Division, Inc., of the American Cancer Society. At this conference the experience of the surgeon, internist, and pathologist was combined with that of the endocrinologist, radiologist, epidemiologist, biochemist, zoologist, virologist, and psychiatrist. The result is a distinguished collection of papers covering almost every important facet of the problem of breast cancer. The contributors are outstanding authorities in their respective fields of special interest.

The book is divided into four sections which consist of Basic Biology I, Definitive Treatment, Basic Biology II, and Hormonal Therapy, each of which is followed by a spirited, informal, but informative panel discussion. It is of interest to note that even experts in their own specialty are often in disagreement.

This book contains a short bibliography of each subject and an excellent summation and index.

Segaloff and his Committee are to be congratulated for this fine presentation of pertinent material which brings into one orbit the satellites of many specialties. In the distressingly slow count-down to the solution of the cancer problem this type of collaborative effort among several scientific disciplines should ultimately prove to be highly rewarding. *—Edward F. Lewison.*

THE VOLUME entitled *Recent Advances in Surgery*[8] was published to commemorate the seventieth birthday of Emil K. Frey, distinguished German surgeon and Chief of Surgery in the University Clinics of the University of Munich Medical School. Prof. Dr. med. Frey, a pupil of Sauerbruch, has been active in practical, academic, and investigative surgery at the Universities of Berlin, Duesseldorf, and Munich. The wide scope of his work includes pioneering of primary closure of open cerebral injuries during World War I; discovery of the pancreatic hormone, kallikrein, in 1927; successful ligation of a patent ductus in 1938, 1 year before the report of Gross and Hubbard.

Equally wide in scope, this volume includes essays depicting recent advances in general and abdominal surgery, anesthesia, vascular surgery, and pathophysiology, neurosurgery, thoracic surgery, urology, reconstructive surgery, and orthopedics. The distinguished contributors represent the leading names in

[6] TEMPORAL LOBE EPILEPSY. Edited by Maitland Baldwin, M.D., and Pearce Bailey, Ph.D., M.D. Co-Editors Cosimo Ajmone-Marsan, Igor Kletzo, and Donald Tower. 581 pages, illustrated. $15.50. Springfield, Ill.: Charles C Thomas, 1958.

[7] BREAST CANCER. The Second Biennial Louisiana Cancer Conference, New Orleans, January 22-23, 1958. Edited by Albert Segaloff, M.D. 257 pages, 43 illustrations. St. Louis: C. V. Mosby Co., 1958.

[8] LEISTUNGEN UND ERGEBNISSE DER NEUZEITLICHEN CHIRURGIE. Edited by Prof. Dr. med. Karl Vossschulte. 339 pages, illustrated. $20.00. Stuttgart: Georg Thieme, 1958.

German surgery and include: Felix (Berlin), Vossschulte (Giessen), Boeminghaus (Duesseldorf), Buerkle de la Camp (Bochum), Dick (Tuebingen), Bronner and Maurer (Munich), Zenker and Haberer (Marburg), Hegemann (Erlangen), and many others. The international character of this book is emphasized by contributions from London (Mason), Alexandria (Hess), Tokyo (Miyamoto), Basel (Nissen), Zuerich (Deucher), and Stockholm (Lund).

The content of the essays varies from original research contributions to collective reviews, from description of original surgical techniques to evaluation of established surgical procedures and their results.

Among some of the very interesting and outstanding contributions are: a kallikrein symposium by Golenhofen, Hensel, Papenberg (Marburg), Forell, Werle, Fogel (Munich), Kraut, Koerbel-Enkhardt (Dortmund), Hollwich, Wethmar (Frankfurt), and Lund (Stockholm). They report original experimental and clinical research with this enzyme. As padutin this enzymatic substance is being used for vasodilatation in peripheral vascular disorders with varying success. Especially interesting is the observation that kallikreinogen (inactive kallikrein) is present in the urine of patients with kidney, and especially tubular, disease. Normally, the active form, kallikrein, is present in the urine. This discussion of enzyme pharmacology and peripheral vascular physiology, while outside the strictly surgical limits of the book, honors Frey as the discoverer of kallikrein, and reflects his wide interests.

Toennis and Walter (Cologne) present sizeable series of cerebral hemangioma (arteriovenous angioma) treated with total extirpation of the lesion, and point out the low mortality and good permanent results. The authors emphasize the definitive treatment and warn against carotid artery ligature or local ligature of tumor supplying vessels. These procedures in the authors' hands give only palliative results at the best and are generally unsatisfactory.

Pia (Giessen) reviews a surprisingly large series of intracranial hemorrhage in childhood, and stresses the subdural hematoma or hydroma as a typical lesion of the early age. He reviews the diagnosis, pathology, and treatment of this important condition.

Maurer (Munich) presents 648 repairs of peripheral nerve injuries, discusses details of the technique, indications, and results.

Hess (Alexandria, Egypt) gives an outstanding discussion of plastic reconstruction procedures on biliary ducts. Techniques are compared and his own results reported. Bronner (Munich) reports a new repair for complete tear of the Achilles tendon. And, last but not least, Dick (Munich) reviews the present day status of hand surgery, pleads for meticulous techniques, delicate handling of tissues, careful and intelligent indications, and for honest appraisal of results. He also stresses the tremendous importance of full time specialization in this "specialty within a specialty" and calls for surgeons dedicated to the surgery of the hand. In this article homage is given to the pioneers of hand surgery: Bunnell, Mason, Iselin, Moberg, and others.

This anniversary issue represents a valuable cross section of all fields of modern surgery and will be an important addition to the library of every physician with surgical interests. —*Gunars Medins.*

THE GROWING COMPLEXITY of obstetrics is attested to by the fact that the first edition of *Obstetrical Practice* was distinctly the product of one man, whereas the seventh edition[9] is a joint undertaking. Further, as the authors state, they have secured expert consultation on their manuscript in certain specialized areas. While the emphasis in the text is on practice, as it has been in previous editions, some sections delve more deeply than others into the fundamentals underlying the applied art. This inconsistency of treatment is probably an inevitable consequence of multiple authorship. Fortunately, there is uniformity in the recommendation of safe, conservative, and, in respect to some problems, what will appear in the eyes of many, old-fashioned obstetrics. The excellent semidiagrammatic illustrations which have long characterized this text are retained, and the cost of the volume is commendably low. Regrettably, there are many errors in the bibliographies. —*Irwin H. Kaiser.*

A TEXT successfully designed to summarize and place on a broad foundation our current knowledge of the role of the endocrine organs in the reproductive processes is entitled *The Endocrinology of Reproduction.*[10] The classification of the context of the book lies somewhere between the gynecologic and urologic textbooks and the literature dealing with endocrinology. The size of this volume, the detailed, yet in many respects fragmentary, knowledge contained foretells the expanding future and the present day complexity of this segment of medicine. The authors are men whose own investigations have demanded wide knowledge of the subjects in their assigned chapters.

The book is divided into four sections: fundamentals, in which genetics, embryology, chemistry, and physiology are reviewed; female endocrinology; male endocrinology; and the effects of aging on reproduction.

The section on fundamentals is unique in that it successfully correlates into digestible reading the very rapidly accumulating data in this area. This is achieved by beginning with the historical background and carrying through to the recent experimental work. The section on genetics is informative and stimulating for the many of us who are not well versed in this field. Cohen's discussion of the chemistry of these hormones is quite clear and can give the reader a strong foundation of understanding in this area.

For the gynecologist reading the section on female endocrinology, by Velardo, is particularly rewarding. The material is well organized, clearly and concisely written, and correlates harmoniously both fundamentals and clinical observations. In controversial areas, conclusions are wisely avoided and experimental data are presented for the reader's decision. The bibliography in all chapters is massive and there is a

[9] OBSTETRICAL PRACTICE. By Alfred C. Beck, M.D., and Alexander H. Rosenthal, M.D. 7th ed. 1115 pages, 952 illustrations. $14.00. Baltimore: Williams & Wilkins Co., 1958.

[10] THE ENDOCRINOLOGY OF REPRODUCTION. Edited by Joseph Thomas Velardo. 340 pages, illustrated. $15.00. New York: Oxford University Press, 1958.

strong emphasis on the classical and historical contributions.

This text is of primary value for students, residents, and practicing physicians who have a particular interest in acquiring a comprehensive background in reproductive endocrinology. Certain portions should be of interest to all who are involved in fertility problems. —*James Henry Ferguson.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

HEREDITY COUNSELING. A Symposium sponsored by the American Eugenics Society and held at the New York Academy of Medicine Building. Edited by Helen G. Hammons. 112 pages, 1 illustration. $4.00. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Bros., 1959.

MODERN MONOGRAPHS IN INDUSTRIAL MEDICINE. Edited by Anthony J. Lanza, M.D. Industrial Carcinogens. By R. E. Eckardt, M.D., Ph.D., F.A.C.P. 164 pages, illustrated. $6.50. New York and London: Grune & Stratton, Inc., 1959.

MANUAL OF DIFFERENTIAL DIAGNOSIS. By William C. Matousek, M.D. 352 pages. $8.00. Chicago: The Year Book Publishers, Inc., 1959.

INTRODUCTION TO SURGERY. By Virginia Kneeland Frantz, M.D., and Harold Dortic Harvey, M.D. 4th ed. 335 pages, 13 illustrations. New York: Oxford University Press, 1959.

OPERATIVE SURGERY. Edited by Charles Rob, M.C., M.Chir., F.R.C.S., and Rodney Smith, M.S., F.R.C.S. Progress Volume 1958, pages 1–100. General Index, pages 1–76. Illustrated. 3 pounds. London: Butterworth & Co. Ltd., 1958.

BLEEDING ESOPHAGEAL VARICES PORTAL HYPERTENSION. By Hirsch Robert Liebowitz, B.S., M.D. Section on Surgical Treatment in collaboration with Louis M. Rousselot, M.D., M.S.(Surg.), Med. Sc.D.(Surg.), F.A.C.S. With a foreword by Allen O. Whipple, M.D., F.A.C.S. 986 pages, illustrated. $24.50. Springfield, Ill.: Charles C Thomas, 1959.

DISEASES OF THE COLON AND ANORECTUM. Edited by Robert Turell, M.D. Vol. I, pages 1–608. Vol. II, pages 609–1238. Illustrated. $35.00 per set. Philadelphia and London: W. B. Saunders Co., 1959.

THE HAND; ITS ANATOMY AND DISEASES. By John J. Byrne, M.D. 384 pages, 166 illustrations. $10.50. Springfield, Ill.: Charles C Thomas, 1959.

GASTRIC CANCER IN SASKATCHEWAN, 1932–1955. By T. H. Crawford Barclay, Ch.M., F.R.F.P.S.G. 208 pages, illustrated. Saskatchewan: Saskatchewan Cancer Commission, Department of Public Health of Saskatchewan, 1958.

TRAITEMENT CHIRURGICAL DE LA TUBERCULOSE PULMONAIRE ASSOCIÉE AUX PNEUMOCONIOSES DU MINEUR DE CHARBON; (A PROPOS DE 110 OBSERVATIONS). (Thèse pour le Doctorat en Médecine. Faculté de Médecine et de Pharmacie de Lille.) By Claude Gautier. 94 pages, 35 illustrations. Paris-Lille: Imprimerie Taffin-Lefort, 1958.

THE FAMILY MEDICAL ENCYCLOPEDIA. By Justus J. Schifferes, Ph.D. Illustrated by Louise Bush, Ph.D. A Health Education Council Book. 617 pages, illustrated. $4.95. Boston and Toronto: Little, Brown & Co., 1959.

THE PLASMA PROTEINS; CLINICAL SIGNIFICANCE. By Paul G. Weil, B.A., M.D.C.M., M.Sc., Ph.D. 133 pages. Philadelphia and Montreal: J. B. Lippincott Co., 1959.

UROLOGY IN OUTLINE. By T. L. Chapman, Ch.M., F.R.C.S.(Eng.), F.R.F.P.S.(Glas.). 176 pages, 138 illustrations. $6.75. Edinburgh and London: E. & S. Livingstone Ltd., 1959. Baltimore: The Williams & Wilkins Co., exclusive U. S. agents.

A HANDBOOK OF MEDICAL HYPNOSIS; AN INTRODUCTION FOR PRACTITIONERS AND STUDENTS. By Gordon Ambrose, L.M.S.S.A., and George Newbold, M.B., B.S., M.R.C.S., M.M.S.A., D.R.C.O.G., D.C.H. Forewords by William Moodie, M.D., F.R.C.P., D.P.M., and William S. Kroger, M.D. 2nd ed. 276 pages, $6.75. Baltimore: The Williams & Wilkins Co., 1958.

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